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Review Article

Theorizing The Role of Gama Type Endorphins in Schizophrenia and Alcoholism: Promoting Genetic Testing and Attempts at Inducing "Dopamine Homeostasis"

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Abstract

We examine the relationship between substance use disorder (SUD) and schizophrenia, emphasizing the role of dopaminergic neurotransmission and genetic predispositions within the context of Reward Deficiency Syndrome (RDS). Our hypothesis posits that a deficiency in gamma-type endorphins leads to persistent hyperdopaminergic activity, amplifying schizophrenia-related symptoms such as hallucinations. Thus, alcohol use may function as a physiological self-healing mechanism by increasing gamma-endorphin levels, thereby mitigating dopaminergic hyperactivity. Additionally, we propose that the DRD2 Taq1 A2 allele could offer protection against SUD in certain individuals with schizophrenia, whereas the Taq1 A1 allele may heighten susceptibility to SUD due to impaired dopaminergic reward processing. The proposed dual genetic pathways arise from the independent yet interrelated genetic bases of SUD and schizophrenia, both involving the dopamine system. Epidemiological studies reveal that psychiatric comorbidity correlates with heightened psychopathology, risky behaviors, and diminished psychosocial performance. Further advanced research, including neuroimaging, genome-wide association studies (GWAS), and epigenetic analyses, is needed to unravel the dopaminergic mechanisms underlying SUD and schizophrenia. Understanding these genetic links may pave the way for precise interventions tailored to specific subpopulations. The findings extend the conceptualization of RDS as a framework for understanding psychiatric and addictive disorders, reinforcing the critical role of dopamine dysregulation in their etiology.

Keywords: Theorizingl Endorphins; Schizophrenia; Alcoholism; Genetic Testing; Dopamine; Homeostasis

Introduction

This hypothesis arises from the observed high comorbidity between substance use disorder (SUD) and schizophrenia. It builds on the recognized role of dopaminergic neurotransmission in the genetic underpinnings of schizophrenia and its association with genetic susceptibility to Reward Deficiency Syndrome (RDS). The hypothesis suggests that inadequate levels of gamma-type endorphins could contribute to self-healing behaviors, which may present as substance use disorder (SUD) in individuals with schizophrenia. Additionally, the Taq1 A2 allele of the DRD2 gene is suggested to act as a protective factor against the onset of substance use disorder (SUD) in individuals with schizophrenia.

A Brief Synopsis of the Genetic Antecedents of Schizophrenia

Schizophrenia is influenced by complex interactions between multiple genes and environmental factors, characterizing it as a polygenic disorder [1]. Genetic research has aimed to identify subtypes or endophenotypes of schizophrenia to enhance diagnostic reliability. Many genes implicated in psychiatric conditions encode proteins critical to synaptic transmission. These genetic studies face challenges such as ambiguous diagnostic criteria and phenocopies, where schizophrenia symptoms mimic those caused by substance abuse [2].

A range of candidate genes has been identified for schizophrenia, particularly those involved in the development of the mesocortical-limbic system. Promising animal model research highlights genes governing GABA, glutamate, and dopamine pathways. GABA neurons that co-express the calcium-binding protein parvalbumin are linked to glutamatergic metabotropic receptors and dopamine D3 receptors. Other notable genes include those encoding catechol-O-methyltransferase (COMT) and neuroregulators that influence neurotransmitter receptor expression and activation, such as glutamate receptors. Additional significant findings include the gene for dystrobrevin-binding protein (with an unclear brain function), serotonin 5-HT-2A receptor genes on chromosome 13q14-q23, and alpha-7 nicotinic cholinergic receptor subunit genes. Chromosomal breakpoints in DISC1 and DISC2, which are associated with schizophrenia and affective disorders, play a role in neurite growth [3]. Specific chromosomal regions, including but not limited to, 22q12-q13, 8p22-p21, 6p24-p22, 13q14-q32, 5q22-q31, 10p15-p11, 6q21-q22, 15q13-q14, 9q34.3, 4q24-q32, 18 and 1q32-q41, have demonstrated potential associations with schizophrenia. Emerging evidence also links schizophrenia to regions on chromosomes 11q and 14p [3]. The cannabinoid CB1 receptor gene located on 6q14-q15 may affect gene expression throughout brain development.

Hoenicka., *et al.*'s research suggests that allele 4 of the cannabinoid receptor 1 (CNR1) gene microsatellite occurs less frequently in individuals with schizophrenia than in healthy controls. Notably, no differences were observed in relation to SUD within this schizophrenic population, suggesting that variations in the cannabinoid system may independently influence susceptibility to schizophrenia [4].

Schizophrenia has been linked to the single nucleotide polymorphism C957T of the DRD2 gene located on chromosome 11q, with an overexpression of the C homozygote genotype observed in patients compared to controls. This indicates that variations in the DRD2 gene may be a key factor in enhancing vulnerability to schizophrenia [5]. However, dopamine receptor involvement in hyperfunctioning of dopaminergic systems in schizophrenia remains controversial. Among the five primary subtypes of dopamine receptors (D1-D5), D2 receptors are traditionally regarded as the most significant. Evidence suggests that the clinical effectiveness of antipsychotic drugs is linked to their capacity to block D2 receptors, supporting the notion that D2 receptor binding may be both necessary and sufficient for antipsychotic effects [6-16]. However, because the DRD2 gene contains relatively few common polymorphisms within its coding region [15], fewer studies have examined the relationship between DRD2 polymorphisms and antipsychotic drug response compared to the serotonin system. In recent years, D3 and D4 receptors have also been linked to the expression of schizophrenia symptoms [7-9].

Comorbidity of substance use disorder (SUD) and schizophrenia

Clinical and epidemiological studies emphasize the high prevalence of co-occurrence between substance use disorder (SUD) and psychiatric disorders, including schizophrenia. Psychiatric comorbidity in individuals with substance use disorder (SUD) is linked to more severe psychopathology, increased engagement in risky behaviors, greater psychosocial impairment, and a higher likelihood of involvement in violent and criminal activities [17]. Identifying distinct phenotypes responsible for schizophrenia, rather than those mimicking psychotic symptoms induced by substance abuse, remains a challenge [2,16]. The increased prevalence of substance use disorder (SUD) among individuals with schizophrenia is not entirely understood, but it has been suggested that patients may use substances to cope with anxiety and cognitive decline [18]. This pattern of acute self-medication is believed to help alleviate symptoms associated with impaired functioning of the mesocorticolimbic reward system, a condition referred to as "Reward Deficiency Syndrome" (RDS) by Blum and colleagues [19].

Earlier work by van Ree and de Wied [20] presents an intriguing hypothesis about the role of gamma-endorphin in schizophrenia, proposing that shared, yet distinct pathways may explain the overlap between schizophrenia and substance use disorder (SUD). Genetic data strongly suggests that schizophrenia vulnerability is separate from substance use disorder (SUD) vulnerability. In fact, both conditions may coexist with independent, distinct polygenic polymorphisms. However, the dopamine system has been implicated in the development of both SUD and schizophrenia.

Hypothesis

A deficiency in gamma-type endorphins may contribute to sustained dopaminergic hyperactivity, which in turn exacerbates symptoms such as hallucinations observed in schizophrenia [20]. We propose that alcohol-seeking behavior in individuals with schizophrenia and substance use disorder (SUD) may serve, in part, as a physiological self-healing mechanism. This process could be linked to the ability of alcohol to increase gamma-endorphin levels, which are known to alleviate hallucinations [20] (Figure 1).

The hypothesis proposes that the DRD2 gene Taq1 A2 allele may be linked to a subtype of non-SUD individuals with schizophrenia could serve as a protective factor against addiction to alcohol or other substances [21]. Individuals with schizophrenia who develop substance use disorder (SUD) may carry the DRD2 Taq1 A1 allele and/or other polymorphisms associated with reward deficiency syndrome (RDS), leading to hypodopaminergic reward functioning.

Reward Deficiency Syndrome (RDS) and Genetic Vulnerability

Reward Deficiency Syndrome (RDS) was first described in 1996 by Blum's laboratory to characterize behaviors stemming from a common DRD2 gene polymorphism [22,23]. These behaviors include impulsivity, compulsivity, and addiction-related traits [19]. The DRD2 gene, often referred to as the "reward gene," has been

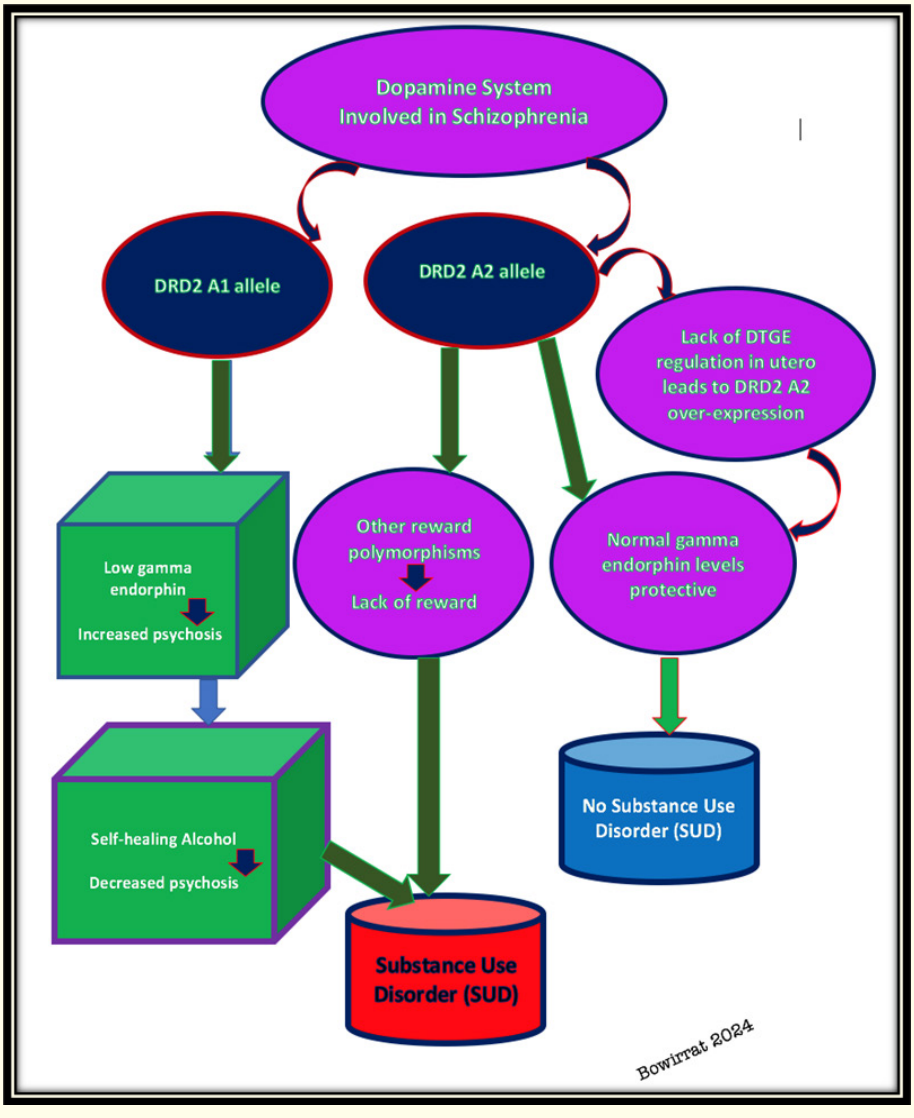

Figure 1: Dopamine and Opioid Peptide Interaction in Schizophrenia and Alcoholism.
Left Side: Carrying the DRD2 A1 allele increases the "wanting" of alcohol, and in individuals with low gamma endorphin (DTGE) levels, this may heighten the risk of psychosis, leading to increased self-medication through alcohol use.

linked to pleasure and is implicated in several neuropsychiatric and addictive disorders [24]. The Taq1 A1 allele, in particular, has been extensively studied and linked to antisocial personality disorder [25], increased novelty-seeking behavior [27], and associated impulsive traits [28].

The mesocorticolimbic dopamine pathway, critical for mediating addiction reinforcement, has been implicated in various psychiatric disorders and addictions [29-32]. Drug-seeking behavior [31,32], a hallmark of RDS, arises when genetic variations disrupt the mesocorticolimbic dopamine reward system [19]. This dysfunction, known as the breakdown of the reward cascade [33-41],

results from a combination of genetic and environmental factors [42] and predisposes individuals to maladaptive behaviors. Psychoactive substances, including alcohol, as well as natural reinforcers like sex, food, gambling, and aggression, stimulate dopamine release in the brain [43-56], alleviating abnormal cravings [46] and enhancing feelings of well-being [57]. A deficiency in D2 receptor density predisposes individuals to a spectrum of addictive, impulsive, and compulsive behaviors [58-60]. Although other neuromodulators such as glutamate, GABA [61], serotonin [62], and enkephalin [63] contribute to the rewarding and stimulating effects of addictive substances, dopamine remains a central role in initiating drug use and relapse after periods of abstinence [63,64-67].

The initial discovery of a positive association between the Taq1 A1 allele of the DRD2 gene and severe alcoholism [24] has spurred numerous studies with both supporting [26,28,30,33,57,65,67-91] and opposing findings [92-105], as highlighted in several reviews [25,58,78,95,105-125]. Research has demonstrated that the Taq1 A1 allele correlates with reduced dopamine D2 receptor density in individuals with alcoholism [72,79,125,127]. However, studies on dopamine transporter (DAT) densities in alcoholics have yielded mixed results [128-132], potentially due to unexamined subtypes within these populations [84,85].

The notion of the dopamine D2 receptor gene as a specific target for alcohol was refuted by Blum., *et al*. [24], who instead proposed that the gene functions as a nonspecific "reward" gene [133]. Additionally, the DRD2 Taq1 A1 allele has been linked to increased sensitivity to stress and anxiety [83,134,135], symptoms often associated with the sensitivity of presynaptic D2 receptors [110]. Sensitivity is higher in individuals with high anxiety compared to those with low anxiety. Beyond substance use disorders, polymorphisms in the DRD2 gene have been implicated in various neurological and psychiatric conditions. These include borderline personality disorder, anxiety, panic attacks, depression, conduct disorder, antisocial personality disorder, and obsessive-compulsive disorder, among others. A comprehensive list of related PubMed articles is available (see Table), categorizing these disorders and their association with dopamine gene polymorphisms, particularly the DRD2 gene. Tabe 1 provides a summary of these associations, with specific data on psychiatric conditions such as borderline personality disorder (4 studies), anxiety (101 studies), panic attacks (10 studies), depression [187], conduct disorder [24], antisocial personality disorder (7 studies), and obsessive-compulsive disorder [38].

Substances and Disorders	Pub Med Listed
Alcohol	460
Caffeine	32
Hallucinogens	31
Inhalants	14
Opioids	213
Sedatives/Hypnotics	11
Stimulants	266
Tobacco/Nicotine	45
Glucose	60
Schizophrenia	826
Reward Deficiency	64
Obesity	129

Table 1: Count of Pub Med listed papers that link various Substance-Related and Reward Disorders and the DRD2 gene polymorphisms (12-25-24).

Table 1 Count of Pub Med listed papers that link various Substance Related and Reward Disorders and the *DRD2* gene polymorphisms as of December 25th 2024.

The association of the DRD2 Taq1 A1 allele and alcoholism presents a significant challenge because the Taq1 A polymorphism is situated more than 10kb downstream from the coding region of the DRD2 gene. This location suggests that a mutation at this site would not directly result in structural changes to the dopamine receptor. It is hypothesized that the Taq1 A polymorphism is in linkage disequilibrium with an upstream regulatory element, a 3′ flanking element, or another gene that influences susceptibility to Reward Deficiency Syndrome (RDS) behaviors. Studies have demonstrated strong linkage disequilibrium between the Taq1 A1 allele and other genetic markers, such as the Taq1 B allele and the SSCP 1 allele [53,70,88,134].

The dopamine D2 receptor has been extensively implicated in various behaviors related to RDS, including alcoholism, nicotine dependence, anxiety, memory deficits, glucose regulation, pathological aggression, pathological gambling, and specific sexual behaviors [24,135]. Among DRD2-related polymorphisms, the Taq1 A restriction fragment length polymorphism (RFLP) has been the most frequently examined. This polymorphism is associated with reduced D2 receptor density, a characteristic linked to addictive and compulsive behaviors. Neville and colleagues identified the "ankyrin repeat" gene (ANKK1), a kinase gene located 10kb downstream from the Taq1 A1 RFLP. ANKK1 contains a serine/threonine kinase domain and is expressed at low levels in the whole spinal cord RNA and the placenta. As a protein involved in signal transduction pathways, ANKK1 plays a role in dopamine regulation and RDS behaviors [136].

The Taq1 A allele of the DRD2 gene represents a single nucleotide polymorphism (SNP) that leads to an amino acid substitution (p.Glu713Lys) within the 11th ankyrin repeat of the ANKK1 protein. Although it is not common for this substitution to disrupt the protein's structural integrity, it may alter substrate-binding specificity. Changes in ANKK1 activity offer an alternative explanation for the previously reported associations between the DRD2 gene and RDS behaviors, as described in earlier studies [136].

Delineating the neural circuitry of rewards is key to deciphering how positive reinforcers motivate behavior [137]. A positive reinforcer is defined as any event that increases the likelihood of a subsequent response, with drugs of abuse often regarded as more potent reinforcers compared to natural rewards such as food and sex [138-140]. The distinction between primary or natural rewards, such as the satisfaction of physiological drives like hunger and reproduction, and secondary or unnatural rewards is crucial. Learned unnatural rewards, such as the hedonic sensations derived from substances like alcohol, gambling, or risk-taking behaviors, play a significant role in shaping behavior [138,141,143].

Reward Deficiency Syndrome (RDS) specifically pertains to inefficiencies or insensitivity in the systems regulating secondary rewards [19,25,28]. This condition includes the compulsive need to escape or avoid adverse effects resulting from cycles of alcohol use [144] and dependence [145-151]. These cycles are associated with dopamine release, which has earned dopamine the nickname of the "pleasure molecule" or "anti-stress molecule" due to its role in mediating pleasure [31,32,83,152]. The neural circuitry involved in positive reinforcement spans several brain regions, including the limbic system and the striatum [59,153-158,201]. The limbic system is responsible for maintaining internal homeostasis, mediating emotional memory and learning, processing emotions, and influencing motivational behaviors, including sexual activity [57,159].

Contrary to earlier assumptions, recent studies have revealed a significant association between the DRD2 A2 allele and the comorbidity of schizophrenia and SUD [17,158-161]. This finding suggests that if the dopamine receptor gene is not central to the substance-seeking behavior observed in this population, alternative pathways contributing to hypodopaminergic reward dysfunction must be explored. Potential contributors include polymorphisms in genes coding for dopamine D1 and D3 receptors, cannabinoid receptors, tryptophan hydroxylase, serotonin receptors, GABA receptors, opioid receptors, dopamine transporters, dopamine beta-hydroxylase, N-acetyltransferase, and Homer 2 proteins [3,162,175]. These genetic variations are all implicated in RDS and may serve as putative drivers of substance-seeking behaviors in affected individuals.

Gamma type endorphins deficiency and increased dopaminergic activity

Pro-opiomelanocortin (POMC) processing produces alpha, beta, and gamma endorphins, which are primarily located in the pituitary but also present in neuronal pathways of the brain. Research has demonstrated that gamma endorphins possess distinct pharmacological properties compared to other endorphins [20]. Certain effects of gamma endorphins occur independently of the opioid peptide systems and their receptors. For example, the removal of the N-terminal group from gamma endorphins eliminates opiate-like actions, creating a peptide called des-tyrosine-gamma-endorphin (DTGE). DTGE exhibits antipsychotic-like properties in various tests. However, as DTGE does not displace haloperidol from its receptor binding site, it has been suggested that DTGE or a similar peptide might act as an endogenous substance with antipsychotic-like effects [176,177].

Gamma endorphins, including DTGE, act as antagonists of dopamine D2 and/or D3 receptors, which are abundant in the nucleus accumbens (NAc), a critical region in the mesolimbic dopaminergic

pathway [178,179]. Endogenous gamma endorphins are thought to regulate dopamine activity, and a chronic deficiency of these peptides-a phenomenon linked to Reward Deficiency Syndrome (RDS)-could lead to sustained hyperdopaminergic activity, as observed in schizophrenia [179]. This hypothesis, which suggests that psychosis in schizophrenia may result from a gamma-endorphin deficiency, has spurred significant research into the antipsychotic effects of these peptides [180-182].

Self-healing using alcohol in people with schizophrenia with SUD

Alcohol abuse in individuals with schizophrenia and substance use disorder (SUD) may partially be explained by gamma endorphin dynamics. Alcohol consumption has been shown to increase gamma endorphin levels in the brain, which could physiologically reduce psychosis in these patients. Animal studies by Jackson et al. revealed that des-enkephalin-gamma-endorphin attenuates the behavioral effects of ethanol [183,184]. This finding supports the notion that alcohol use in a subset of individuals with schizophrenia and SUD may serve as a self-healing mechanism to alleviate psychotic symptoms.

The DRD2 gene Taq1 A2 allele may serve as a protective factor against the development of substance use disorder (SUD), particularly alcohol use, in individuals with schizophrenia

The DRD2 Taq1 A2 allele may protect against the development of substance use disorder (SUD), particularly alcohol dependence, in individuals with schizophrenia. It has been suggested that certain subpopulations of schizophrenic patients carry the DRD2 A2 allele, which could reduce the risk of developing SUD, as the DRD2 A1 allele-but not the A2 allele-has been strongly linked to SUD and other addictive behaviors [18,185,193]. A potential explanation for this protective effect involves the regulatory role of dopaminergic activity during embryonic development. Reduced dopaminergic regulation (i.e., lack of DTGE) could lead to an increase in dopamine release. Consequently, an overexpression of the DRD2 A2 allele might emerge as an adaptive response to balance the hyperactive dopamine system. Noble., *et al*. [72] further noted that D2 receptor density is determined by DRD2 genotypes, with A1/A1 genotypes showing the lowest receptor density, A1/A2 genotypes exhibiting moderate reductions, and A2/A2 genotypes demonstrating the highest receptor density. Thus, the overexpression of the *DRD2 A2* allele could act as a compensatory mechanism to mitigate dopaminergic hyperactivity.

Similar protective genomic adaptations have been observed in other contexts, such as the inactive aldehyde dehydrogenase-2 gene (*ALDH2*). Individuals carrying the *ALDH2*2* allele exhibit minimal or no *ALDH2* enzymatic activity, leading to a buildup of blood acetaldehyde even after consuming small amounts of alcohol. This results in the flushing response, an unpleasant physiological reaction that discourages alcohol consumption [194,195]. This mechanism significantly reduces the risk of alcoholism in these individuals. Although the polymorphic *ALDH2*2* allele is present in ~50% of Chinese and Japanese, it is found in only 10% of those diagnosed with alcoholism in these populations [196,197].

Matsushita., *et al.* [198]. observed that individuals with the *ALDH2*2* allele, whether alcoholics or healthy controls, were more likely to carry the *DRD2 A1* allele than those without the *ALDH*22* allele. This finding suggests that alcoholics who carry the inactive *ALDH2*2* alleles, despite experiencing severe adverse reactions to alcohol, may have an underlying genetic susceptibility toward alcoholism. The possession of the DRD2 A1 allele might represent one such trait.

Additionally, Huang., *et al.* [199] investigated the association between the *DRD2* gene and alcohol-metabolizing genes, such as alcohol dehydrogenase (*ADH1B*) and aldehyde dehydrogenase (*ALDH2*). Both of these genes, alongside their associated polymorphisms, have been implicated as protective against alcoholism and play a role in dopamine metabolism [200,201]. Their findings indicated that the *DRD2 A1* allele was significantly associated with a specific subtype of alcoholics characterized by anxious-depressive traits (ANX/DEP ALC). Furthermore, the relationship between the *DRD2 A1* allele and ANX/DEP ALC appears to be influenced by both the *ADH1B* and *ALDH2* genotypes.

Future perspectives

In the coming years, advancements in genetic research will likely include a greater focus on genome-wide association studies (GWAS), epigenome-wide association studies (EWAS), and neuroimaging techniques to further illuminate the intricate relationship between substance use disorder (SUD) and other psychiatric conditions. While significant research has explored the role of opioid peptides in neurons throughout the nervous system (tel-di-mesrhombencephalon and the spinal cord) [202], not much has been found about their relationship with SUD. The most recent study on

gamma-endorphins and schizophrenia dates back to 2002 [203], despite the availability of 812 PubMed articles on gamma-endorphins [3,9,13]. As early as 1982, it was discovered that des-1-tyrosine-gamma-endorphin (DTGE) produced behavioral effects in rodents similar to those of drugs acting on the central nervous system. These effects were attributed to DTGE's influence on tyrosine hydroxylation in striatal synaptosomes, suggesting its role in dopamine biosynthesis and its potential antipsychotic effects [204].

Interestingly, while DTGE does not exhibit direct in-vitro activity at dopaminergic receptors, it inhibits [3H] spiperone binding in vivo in various brain regions [2-17]. This effect is comparable to that of beta-endorphin [6-17], now recognized as a major DTGE metabolite [205]. Moreover, localized administration of [Des-Tyr1]-gamma-endorphin in regions such as the nucleus accumbens (NAc) or neostriatum replicates the effects of antipsychotics, potentially through adrenocorticotropic hormone (ACTH) and dopaminergic mechanisms [206].

Patients with schizophrenia exhibit behavioral supersensitivity to dopamine-like drugs such as amphetamine and methylphenidate. This phenomenon is supported by evidence of increased dopamine release, a slight rise in dopamine D2 receptors, and an elevation in dopamine D2High receptors [207]. According to Seeman [207], the increase in D2High receptors in schizophrenia parallels findings in various animal models of psychosis. Factors contributing to this supersensitivity may include alterations in D2 receptor phosphorylation, desensitization, attachment of Arestin, receptor internalization, de-phosphorylation rates, receptor dimer formation, and GTP regulation by GTPases. Clinically, haloperidol has been shown to reduce psychostimulant-induced D2High receptor elevation, a finding that holds significance for treating schizophrenia and SUD. Blum et al. proposed a neurobiological and genetic mechanism involving DRD2 supersensitivity in SUD [208].

Research on dopaminergic polymorphisms in psychiatric disorders and substance use disorder (SUD) has been a significant focus since Blum et al. first identified an association between the DRD2 gene and severe alcoholism [24,209,223]. As we enter the genomic era, more profound insights into the role of genetic polymorphisms in schizophrenia and SUD are expected. Research into the effects of antipsychotics on brain function will also expand significantly [224]. However, one area that remains underexplored is the genetic regulation of gamma-endorphins and their association with schizophrenia susceptibility. Future research should prioritize genotyping polymorphisms in gamma-endorphin regulatory genes, including those involved in synthesis, synaptic release, and catabolism, through large-scale case-control studies to uncover their potential role in schizophrenia vulnerability.

Summary

Both Substance Use Disorder (SUD) and schizophrenia are multifactorial conditions influenced by the dopamine system. Studies have shown that the DRD2 A1 allele increases the genetic risk for SUD, particularly alcoholism, while carriers of the DRD2 A2 allele do not face the same risk. One hypothesis suggests that alcohol-seeking behavior in individuals with schizophrenia carrying the Taq1 A1 allele may result from a deficiency in gamma-type endorphins. This deficiency could contribute to the hyperdopaminergic activity seen in these individuals. It is proposed that alcohol use in individuals with schizophrenia could serve as a compensatory mechanism, enhancing gamma-type endorphin activity and thereby decreasing dopamine activity in the nucleus accumbens (NAc).

Additionally, we propose that the DRD2 Taq1 A2 allele could be overexpressed as a compensatory mechanism to counteract dopaminergic hyperactivity due to the absence of DTGE during fetal development. This allele may also be linked to a specific subtype of non-SUD individuals with schizophrenia, potentially acting as a protective factor against addiction to alcohol or other substances. These hypotheses suggest that vulnerabilities to substance use disorder (SUD) and schizophrenia within the dopamine system may arise from two separate sets of genetic associations, indicating the need for further research within distinct subgroups of individuals with schizophrenia.

We advocate research that incorporates neuroimaging, genome-wide association studies (GWAS), and epigenetic approaches to explore the relationship between neurogenetics and systems biology. Such studies could provide valuable insights into the role of dopamine in psychiatric disorders and substance use disorders (SUD).

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Conflict of Interest

There are no conflicts of interest to declare.

Author Contribution

KB wrote the initial draft, and all co-authors significantly edited the entire manuscripts making improvements and approved the final version.

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