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Review

Canonical and Non-Canonical Antipsychotics' Dopamine-Related Mechanisms of Present and Next Generation Molecules: A Systematic Review on Translational Highlights for Treatment Response and Treatment-Resistant Schizophrenia

Andrea de Bartolomeis *, Mariateresa Ciccarelli, Giuseppe De Simone, Benedetta Mazza, Annarita Barone and Licia Vellucci

Section of Psychiatry, Laboratory of Translational and Molecular Psychiatry and Unit of Treatment-Resistant Psychosis, Department of Neuroscience, Reproductive Sciences and Dentistry, University Medical School of Naples "Federico II", 80131 Naples, Italy
* Correspondence: adebarto@unina.it; Tel.: +39-081-7463673

Abstract: Schizophrenia is a severe psychiatric illness affecting almost 25 million people worldwide and is conceptualized as a disorder of synaptic plasticity and brain connectivity. Antipsychotics are the primary pharmacological treatment after more than sixty years after their introduction in therapy. Two findings hold true for all presently available antipsychotics. First, all antipsychotics occupy the dopamine D2 receptor (D2R) as an antagonist or partial agonist, even if with different affinity; second, D2R occupancy is the necessary and probably the sufficient mechanism for antipsychotic effect despite the complexity of antipsychotics' receptor profile. D2R occupancy is followed by coincident or divergent intracellular mechanisms, implying the contribution of cAMP regulation, β-arrestin recruitment, and phospholipase A activation, to quote some of the mechanisms considered canonical. However, in recent years, novel mechanisms related to dopamine function beyond or together with D2R occupancy have emerged. Among these potentially non-canonical mechanisms, the role of Na^{2+} channels at the dopamine at the presynaptic site, dopamine transporter (DAT) involvement as the main regulator of dopamine concentration at synaptic clefts, and the putative role of antipsychotics as chaperones for intracellular D2R sequestration, should be included. These mechanisms expand the fundamental role of dopamine in schizophrenia therapy and may have relevance to considering putatively new strategies for treatment-resistant schizophrenia (TRS), an extremely severe condition epidemiologically relevant and affecting almost 30% of schizophrenia patients. Here, we performed a critical evaluation of the role of antipsychotics in synaptic plasticity, focusing on their canonical and non-canonical mechanisms of action relevant to the treatment of schizophrenia and their subsequent implication for the pathophysiology and potential therapy of TRS.

Keywords: treatment-resistant schizophrenia; antipsychotics; postsynaptic density; dopamine; glutamate; synaptopathy; PSD-95; Homer

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1. Introduction

Dopamine cortical–subcortical dysregulation epitomizes the main, albeit not the only, neurotransmitter landmark of schizophrenia pathophysiology and antipsychotics remain, more than sixty years after their introduction in therapy, the cornerstone of schizophrenia treatment.

Emerging findings from novel methodologies of receptor–ligand computational and Fluorescence Resonance Energy Transfer (FRET) microscopy modeling at the dopamine D2 receptor (D2R) [1], analysis of antipsychotics effects on quantal dopamine release at the presynaptic site [2], and in vivo studies of dopamine metabolism by Positron Emission Tomography (PET) imaging have unveiled previously unexplored landscape of antipsychotics—dopamine dynamics [3]—calling for a re-evaluation of the canonical dopamine-based mechanism of this class of drugs [4].

Antipsychotics are the mainstay of the pharmacological treatment of schizophrenia and are also prescribed for mania in bipolar disorder as well as, to a lesser extent, augmentation therapy in treatment-resistant depression. Preclinical, clinical, and human functional studies strongly support the occupancy of D2R as a common, necessary, and perhaps sufficient mechanism of action (MOA) for all molecules available at present in clinics, even if they are characterized by different receptor profiles. This mechanism is coherent with a "dopaminocentric hypothesis" of psychosis that was conceptualized almost 50 years ago and is still considered fundamental [5–7], even if relevant updates and revisitation of findings from imaging [8–10], post-mortem [11,12], and modeling studies [13] have incorporated other neurotransmitter mechanisms, primarily the glutamatergic ones. However, the same findings call for a more stringent re-evaluation of antipsychotics' MOA within the dopamine system, starting from the main target: the D2R. A critical appraisal of the non-canonical dopamine effects of antipsychotics is not only of significative heuristic value but even more relevant for the translational possibility of exploring novel therapeutic strategies.

Novel strategies are even more needed with reference to those patients who do not respond to treatment with antipsychotics using at least two antipsychotics (one should be an atypical or new generation drug) at a dose of 600 mg/equivalent of chlorpromazine for at least 6 weeks of treatment, these patients are defined as treatment-resistant [14]. The only available drug for these patients is, after more than fifty years, clozapine.

Considering that (i) at present, the dopaminergic strategy to tackle psychosis has been demonstrated to be effective, at least for positive symptoms, (ii) D2R occupancy could be limited by the potential onset of motor and other adverse events, and (iii) multiple domains of the disorder are indirectly related to dopamine through its modulation by other neurotransmitters systems, we addressed the following questions:

(1) Is there space for more dopaminergic strategy beyond dopamine D2R occupancy in psychosis treatment?
(2) If antipsychotics tune the dopaminergic system by mechanisms other than the non-direct D2R-mediated one, what are the other non-canonical dopaminergic targets?
(3) How do antipsychotics acting at D2R impact trans-synaptically other neurotransmitter systems, as well as synaptic and meta-synaptic plasticity?
(4) Finally, how the next generation of antipsychotics now appearing on the landscape of schizophrenia treatment may regulate the dopaminergic system?

With these questions in mind, we have addressed the background and the potential relevance for the therapy of non-canonical molecular effects of antipsychotics considering the complexity of antipsychotics' multiple receptors profile in the framework of a dopaminergic MOA within and beyond dopamine D2R occupancy.

2. Materials and Methods

The bibliographic search and selection process was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. The search was carried out on three different databases (EMBASE, Scopus, and PubMed) on 9 December 2022 and was updated on 18 January 2023, before the final writing of the manuscript. It was conducted using the following search string: ((((((((((((Dopamine[Title/Abstract]) OR (dopamine transporter[Title/Abstract])) OR (tryosine 3-monooxygenase[Title/Abstract])) OR (dopamine receptor*[Title/Abstract])) OR (dopa decarboxylase[Title/Abstract])) AND (mechanism of action[Title/Abstract]))))) OR (antipsychotic* agent*[Title/Abstract])) AND (postsynaptic density[Title/Abstract])) OR (postsynaptic density protein*[Title/Abstract])) OR (presynaptic terminal*[Title/Abstract])) AND (schizophrenia[Title/Abstract])) OR (treatment-resistant schizophrenia[Title/Abstract]), and retrieved records and full texts were managed by using Endnote X9 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. Additional documents were obtained by hand-searching the reference lists of enclosed items with a focus on antipsychotics' unconventional MOA and possible druggable targets as a therapeutic strategy in schizophrenia and treatment-resistant

schizophrenia (TRS). In addition, after reading the entire article, other cross-references have been included. Although this second typology of the search may introduce some differences in the methodology of PRISMA, we believe that the overall strategy used in this translation review linking preclinical and clinical data is the best fit possible to further investigate the canonical and non-canonical antipsychotics MOA in schizophrenia treatment that could be overlooked with a strict systematic search. We considered eligible for the study: English-written in vitro or in vivo, both animal models or human studies, published in peer-reviewed journals that focused on the canonical and non-canonical effects of antipsychotics and putative MOA relevant for schizophrenia treatment and treatment resistance. Furthermore, no time restrictions were enforced, and original clinical and preclinical studies and reviews were included. Conference abstracts and commentaries were excluded. The review protocol is now available on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY202310079).

3. Results

The PRISMA flow chart has been reported in Figure 1. The search returned a total of 3427. The papers were first evaluated by title/abstract by two independent researchers (LV and MC), and then relevant articles were selected for full-text evaluation based on the eligibility criteria. Inconsistencies were resolved by consensus in a meeting with another researcher (GDS), and the final critical assessment of relevant articles was performed by a second consensus meeting with a board review including all of the authors. Finally, 95 articles were included in the qualitative synthesis. In the following sections, we performed a critical appraisal of the results by analyzing the potentially significant value as a non-canonical (i.e., non-conventional) MOA of antipsychotics in the framework of the dopaminergic system.

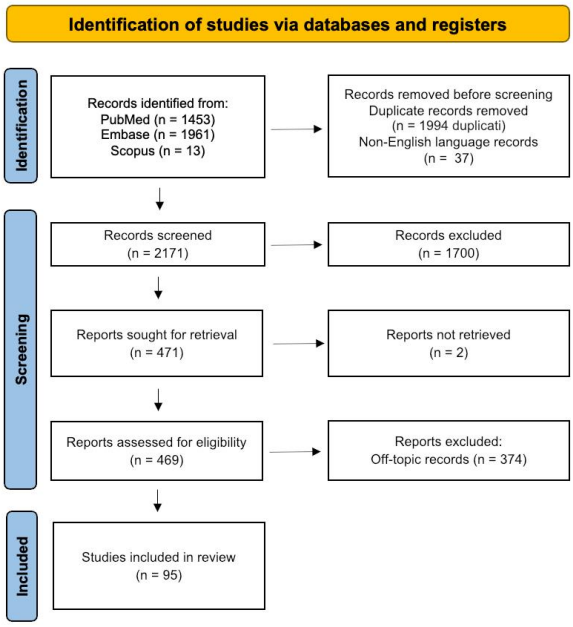

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart [15].

3.1. Dopamine Receptors and Transporters: Canonical and Non-Canonical Mechanism of Action Relevant for Schizophrenia and Treatment-Resistant Schizophrenia

3.1.1. Dopamine D2 Receptors: Relevance for Treatment-Resistant Schizophrenia and Putative Link with Dopamine Supersensitivity Psychosis

Dopamine dichotomic cortical–subcortical involvement in schizophrenia pathophysiology, may suggest the coexistence of cortical "hypodopaminergia" and subcortical "hyperdopaminergia" associated with the dysfunction of other neurotransmitter systems, mainly serotonergic and glutamatergic ones [16,17]. Treatment with antipsychotics occupying mainly, if not exclusively, the D2R, may counterbalance the hyperdopaminergic state, es-

pecially at the striatal level, which is considered the rationale behind antipsychotic action. However, the blockade of D2Rs in the mesocortical, nigrostriatal, and tuberoinfundibular pathways has also been linked to several side effects, such as worsening of cognitive and negative symptoms, extrapyramidal symptoms (EPS), and hyperprolactinemia [18]. Furthermore, it has been proposed that the sustained occupancy of D2Rs could potentially be linked to antipsychotic tolerance, dopamine supersensitivity psychosis (DSP), and tardive dyskinesia (TD) [19]. The mechanisms underlying DSP and TD have been associated with long-term blockade of D2R, leading to upregulation of the receptors, an increase in D2R density, and/or a shift from a "low affinity" to a "high affinity" state [20,21], potentially resulting in "dopamine supersensitivity".

Iyo and coworkers hypothesized that there is an optimal range in the number of D2Rs available for dopamine binding to achieve adequate treatment in patients with schizophrenia [20]. The authors estimated the optimal D2R occupancy by assuming that the plasma range of antipsychotics was constant while the D2R density varied. The results showed that the plasma level of antipsychotics increased and decreased along with D2R density, estimating that the optimal D2R occupancy range was 65% to 78%, rising to a range of 82% to 89% with increased receptor density, and 42% to 63% with decreased receptor density [20]. The results also indicated that the reduction in the plasma level of antipsychotics was greater in patients with higher D2R density, as they needed increased doses of antipsychotics to achieve optimal receptor occupancy. On the other hand, in patients with lower D2R density, a reduced dose of antipsychotic could achieve optimal receptor occupancy, resulting in liability for extrapyramidal symptoms (EPS) [20]. Kruyer and coauthors have recently demonstrated that behavioral supersensitivity could be related to long-lasting synaptic plasticity processes at pre-, peri-, and postsynaptic sites, which includes the insertion of Ca^{2+}-permeable α-ammino-3-idrossi-5-metil-4-isossazol-propionic acid receptors (AMPARs) and the loss of inhibitory postsynaptic currents (IPSCs) dependent on D2R in the middle spiny neurons of the *nucleus accumbens* (NAc) [22]. These findings underlined hyperexcitability causing locomotor sensitization associated with behavioral endophenotypes of resistance to antipsychotic treatment. In this context, the chemogenetic restoration of inhibitory postsynaptic currents in D2R could prevent antipsychotic-induced supersensitivity [22]. Furthermore, an inflammatory-based mechanism implicated in DSP development could be related to oxidative stress resulting from free radicals released by dopamine metabolism. Indeed, dopaminergic neurons in the *substantia nigra* are sensitive to reactive oxygen species (ROS) and to the dysregulation of cellular redox homeostasis generated by catecholamine metabolism [23], which is possibly relevant for TD. There is evidence of increased oxidative stress caused by lipid peroxidation associated with neuronal damage in patients with TRS compared to those responsive ones, potentially significant for DSP and TD [24]. Preclinical studies in rats have shown that neuroleptic-induced TD is also associated with changes in the expression of serotonin 5-HT_2 receptors (5-HT_2Rs) [25]. Antipsychotic treatment may reduce the density of 5-HT_{2A}Rs in the prelimbic cortex and NAc while increasing their density in the caudate-putamen. Therefore, 5-HT_{2A}R activation is necessary for the full expression of DSP induced by antipsychotics, modulating dopamine-dependent behavior. These effects are potentially related to changes in 5-HT_{2A}R density in the prefrontal cortex (PFC) and striatum, suggesting the role of the 5-HT_{2A}R blockade in the regulation of antipsychotic-induced DSP. Moreover, a mechanistic link has been proposed between the development of TD and serotonin 5-HT_6R in patients with Parkinson's disease and transplanted with dopaminergic neurons. The 5-HT_6R could be implicated in the dopamine release responsible for the "transplant-induced dyskinesia" side effect induced by the inhibition of autoreceptor feedback [26]. For selective high-affinity D2R antagonism, both clinical and preclinical studies have found an association between poor cognitive performance mediated by the disruption of D2R-mediated signaling [27], particularly in the PFC [28]. D2R activation has also been shown to be relevant to dopamine uptake by vesicular monoamine transporter-2 (VMAT-2) [29], suggesting that its pharmacological modulation may be a non-canonical therapeutic target in the treatment of schizophrenia [30]. Despite the elusive neurobiology of DSP, few lines of evidence may suggest a link with TRS [31]. Pharmacogenetics studies have demonstrated

a significant relationship between the *DRD2* gene polymorphism -141 C Ins/Del and poor response to antipsychotics [32,33], suggesting the contribution of D2R in the development of DSP and TRS [31,34].

At the molecular level, the mechanisms responsible for D2R trafficking could contribute to DSP [35]. β-arrestin 2 (ARRB2) is directly responsible for internalizing D2R phosphorylated by G protein-coupled receptor kinase 6 (GRK6) and may activate the cellular signaling mediated by the AKT/PP2A/ARRB2 complex, resulting in delayed signaling compared with early G-protein-mediated signaling [36,37]. In addition, the absence of ARRB2 promoted the early G protein pathway by disrupting delayed G-protein-independent signaling [36,37]. Furthermore, D2R partial agonist antipsychotics are responsible for counterbalancing phencyclidine (PCP)-induced hyperlocomotion in wild-type mice, but this effect is lacking in *ARRB2*-knock out (KO) mice [38], indicating a crucial role of ARRB2 signaling in D2R-mediated antipsychotic effects [38]. PCP is involved in developing psychotic and negative symptoms of schizophrenia in healthy individuals [39–42] and in the exacerbation of these symptoms in schizophrenic patients [43,44]. It has been suggested that GRK6 and ARRB2 might regulate D2R in a low-affinity state for dopamine [45], whereas the GRK6/ARRB2 system was found altered and unable to internalize D2R in the rat DSP model, suggesting that alteration of the GRK6/ARRB2 system has an impact on the pathogenesis of DSP and treatment resistance [34,35].

There is growing evidence that antipsychotics could act as chaperones in the trafficking of dopamine receptors from the intracellular site to the membrane surface; however, not all antipsychotics are equal regarding this feature. Aripiprazole and clozapine have less propensity to act as chaperones of D2R, preventing their translocation and possible upregulation to the cell surface, therefore, this differential mechanism may represent a putative non-canonical MOA to reduce the onset of DSP [46,47].

3.1.2. The "Other" Dopamine D2-like Receptors, Dopamine Non-D2 Receptors and Their Non-Canonical Position in Antipsychotics' Mechanism of Action

The Dopamine D3R

Even though all antipsychotics occupy both D2R and D3R, the role of the latter one has received less attention in the past, probably for the reported low density and more restricted distribution in a few brain regions. However, more recently, a growing interest at both clinical and preclinical levels has considerably changed the appraisal of the D3R in the framework of antipsychotic therapy. At the clinical level, the introduction of cariprazine has significantly marked the role of dopamine D3R as a relevant addition to the schizophrenia pharmacological armamentarium. Cariprazine is the first available antipsychotic that preferentially acts as a partial agonist at D3R, with K_i = 0.085 nM, higher than the one for the D2R (K_i = 0.49 nM) [48], demonstrating significantly better efficacy on prevalent negative symptoms in schizophrenia patients compared to a full D2R antagonist, such as risperidone [49,50]. At the preclinical level, the D3R occupancy could be implicated in antipsychotic and pro-cognitive effects [51–53] by increasing acetylcholine release in the PFC by disinhibiting the activity of dopaminergic neurons projecting to the NAc or PFC, or by activating cAMP response element-binding protein (CREB) signaling in the hippocampus [54]. Of interest, the genetic disruption of the dysbindin gene (*DTNBP1* gene), one of the top candidate genes associated with schizophrenia, affects the intracellular trafficking of D3R. Notably, in both schizophrenia and genetic animal model of the disorder, the concomitant reduction in D3R and *DTNBP1* gene expression was associated with pro-cognitive effects. The D3R/dysbindin interaction has been shown to promote D2R/D3R imbalance by favoring an increase in D2R signaling in the PFC but not in the striatum [55], underlining the potential role of regional D2R/D3R reciprocal ratio of occupancy and D3R antagonism in improving cognitive symptoms in schizophrenia. D3R signaling is emerging as a possible regulatory mechanism of parvalbumin neuron-dependent gamma oscillations (γ-oscillations are believed to be a major organizer of brain functional networking [56] and have been demonstrated to be abnormal in schizophrenia patients [57]). γ-oscillations are 30-90 Hz bursts mainly generated in the cortical–subcortical brain regions,

mainly by parvalbumin-positive γ-aminobutyric acid (GABA) interneurons, on the other side, have been demonstrated to be abnormal in post-mortem studies on schizophrenia patients, and animal modeling γ-oscillations have been shown to be deranged by N-methyl-D-aspartate receptor (NMDAR) blockade [58].

The Dopamine D4R

D4Rs are predominately located in the prefrontal and temporal areas, sparing the basal ganglia, whereby compounds with a higher affinity for D4Rs than D2Rs could selectively reduce dopaminergic tone in the mesolimbic and mesocortical systems without affecting the nigrostriatal pathway and not producing motor side effects [59]. Furthermore, as D4Rs localized on both pyramidal and GABAergic neurons in the cortex, hippocampus, thalamus, *globus pallidus*, and *substantia nigra* [60], it has been hypothesized that selective D4R antagonists could, directly and indirectly, modulate glutamatergic transmission [60]. D4R seems to also be involved in the restoration of γ-oscillation in the hippocampal slices of aged mice brains, probably with a therapeutic effect on cognitive impairment related to ageing [61]. This effect is reported in hippocampal parvalbumin-positive GABA interneurons and parvalbumin-positive basket cells, which are critical for γ-oscillations, by double *in situ* hybridization and immunofluorescence histochemistry, confirming the crucial role of D4R in cognitive deficits [62].

A potential difference between atypical and typical antipsychotics could concern binding to the D4R, considering that many atypical antipsychotics show a slightly higher affinity for D4R than D2R, whereas the majority of typical antipsychotics have a higher affinity for D2R than D4R [63]. Despite this observation, the affinity for D4R used as a single measure cannot distinguish between typical and atypical antipsychotic drugs [63]. It is possible that antagonism at D4R and 5-HT_{2A} produces discriminative stimulus effects of "atypicality" similar to clozapine, but the additional antagonism at D2R makes it similar to typical antipsychotics [64]. It is noteworthy that the antipsychotic clozapine may interact with D4R concerning its tolerability profile and adverse effects. Indeed, the 120 bp duplication in the *DRD4* gene is significantly associated with clozapine-induced sialorrhea, suggesting that this duplication may increase the risk of sialorrhea in TRS patients treated with clozapine [65].

The Dopamine D1R

Dopamine D1R and related intracellular signaling have been longly considered a complex puzzle in the dynamic of dopamine under antipsychotic treatment [66]. One major issue is that the increased release of dopamine in schizophrenia is supposed to hit both classes of dopamine receptors, D1- and D2-like, and on the other side, all antipsychotics, with few exceptions (asenapine and clozapine), have relatively low affinity for D1R compared to D2R affinity and occupancy/antagonism. Therefore, D1R remains, except for asenapine and clozapine, a "black spot" in the dopaminergic-related effects of antipsychotics in terms of efficacy. Despite the low D1R affinity of antipsychotics, recently, some non-canonical mechanisms have emerged supporting an indirect role of D1R in antipsychotics action among, for example, chlorpromazine, a D1R-like inverse agonist in the mouse brain, which reduces $Ca_{v2.2}$ currents by occluding D1R-like constitutive activity [67,68]. Moreover, the evidence that D1R- NMDAR reciprocal interaction, especially in the NAc, is involved in behavioral preclinically relevant for schizophrenia modeling prepulse inhibition (PPI) [69], suggests the possibility that D1R may be manipulated by acting on NMDAR. Lynch and co-workers proposed that dopamine hypoactivity in the NAc could be behind the negative symptoms of schizophrenia and that treatments with low-dose dopamine agonists could mimic the behavioral profile of negative symptoms via direct stimulation of D1Rs in the PFC [70]. Accordingly, clozapine's efficacy for negative symptoms could be partially ascribed to the blockade of D1Rs in the PFC, resulting in enhanced dopaminergic activity in the NAc favored by glutamate [70]. Indeed, binding assays showed that clozapine has a higher affinity for D1Rs than D2Rs [71], acting preferentially on D1Rs localized in the frontal cortex instead of in the striatum, hypothesizing a regional selectivity based on its receptor peculiarity [72].

Preclinical studies reported that clozapine suppressed the acute increase in medial PFC glutamate levels by enhancing NMDAR-mediated neurotransmission that was not induced by D1R-dependent dopaminergic neurotransmission, partially explaining the clozapine-induced attenuation of hyperlocomotion in PCP-treated rats [73].

However, the results of clinical trials with selective D1R antagonists do not show antipsychotic responses in patients [74]. A different look at D1R in terms of antipsychotic response comes from the co-expression of D1R with D2R, which has been shown to increase the affinity of clozapine for D1R [75]. A variable distribution of medium spiny neurons co-expressing D1R and D2R in the basal ganglia has been reported, with the highest incidence in the NAc and *globus pallidus* and the lowest incidence in the caudate putamen [76]. It has been hypothesized that D1R-D2R heterodimers located in cell bodies and presynaptic terminals promote grooming behavior and attenuate α-Amino-3-Idrossi-5-Metil-4-isoxazolone propionate receptor (AMPAR) GluR1 phosphorylation by regulating calcium/calmodulin kinase II (CAMKII) signaling directly in the NAc [76]. D1R-D2R heterodimer formation and functional activation in the *globus pallidus* are increased in schizophrenia [76,77] and are at least in part supported by the increase in the affinity of clozapine for D1R in the heterodimers [75] (Figure 2). Further research on the putative role of D1R/D2R heterodimers and potential exploitation for bypassing the poor response to conventional antipsychotics in TRS is warranted.

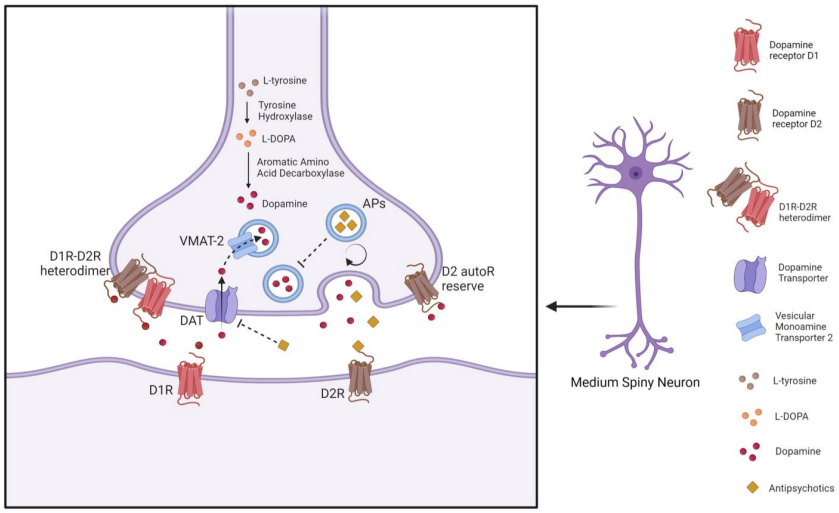

Figure 2. Presynaptic dopaminergic terminals and dopamine transporter in schizophrenia. The co-expression of D1R-D2R heterodimers at the presynaptic terminals in medium spiny neurons regulating calcium/calmodulin kinase II signaling directly in the *nucleus accumbens* [76]. The antipsychotic mechanism of action involving the presynaptic dopaminergic terminal. In this regard, preclinical studies showed that antipsychotics could accumulate in the synaptic vesicles resulting in a significant release of extracellular drug concentrations that inhibit presynaptic function [78,79]. Treatment with antipsychotics could generate an intracellular drug store co-released by vesicles together with endogenous dopamine, resulting in the inhibition of presynaptic voltage-gated sodium channels, which regulate dopamine release with an autoinhibitory effect. The formation of a 'reserve' of presynaptic D2 autoreceptors that interact mainly with endogenous dopamine, whereas postsynaptic D2Rs could be mostly occupied by antipsychotics. The blockade of DAT has been responsible for the restoration of synaptic dopamine levels in chronic treatment with antipsychotics. Dopamine uptake by VMAT-2 showed to be relevant to D2R activation, suggesting its pharmacological modulation as a therapeutic target in schizophrenia. L-DOPA, Levodopa; D1R, Dopamine receptor D1; D2R, Dopamine receptor D2; DAT, Dopamine transporter; VMAT-2, Vesicular monoamine transporter 2; APs, Antipsychotics; D2 autoR, Dopamine D2 autoreceptor. Created with BioRender.com on 7 March 2023.

3.1.3. The Role of Presynaptic Dopaminergic Terminals and Dopamine Transporter

Clinical studies have estimated that the time course of D2R occupancy in the living human brain achieves adequate central D2R blockade within hours of antipsychotic administra-

tion, whereas the appreciable antipsychotic effect appears after days or weeks of treatment [80]. However, the delayed clinical antipsychotic effect can be explained both by the drug's action at postsynaptic D2R and its MOA at the presynaptic dopaminergic terminal. In this regard, preclinical studies showed that weak-base antipsychotics (e.g., haloperidol, chlorpromazine, clozapine, and risperidone) could accumulate in the synaptic vesicles of presynaptic dopaminergic terminals, resulting in a significant release of extracellular drug concentrations that inhibit presynaptic function in an activity-dependent manner [78,81] (Figure 2). In this context, it has been proposed that released levels of antipsychotics may recycle with synaptic vesicles by exerting an autoinhibitory effect on vesicular exocytosis, promoted by inhibition of voltage-gated sodium channels (VGSCs) and dependent on the intensity of stimulation, regulating synaptic transmission [78]. Therefore, treatment with antipsychotics could generate an intracellular drug store co-released by vesicles together with endogenous dopamine, resulting in the inhibition of presynaptic VGSCs, which in turn regulate dopamine release with an autoinhibitory effect [78]. Another antipsychotic MOA hypothesized the formation of a "reserve" of presynaptic D2R autoreceptors while postsynaptic D2Rs would be instead occupied by antipsychotics. Endogenous dopamine would thereby mainly interact with D2 autoreceptors, reducing the presynaptic synthesis and release of dopamine and leading to an indirect antipsychotic effect [5]. However, it has been shown that the initial increase in synaptic dopamine availability after exposure to antipsychotics may decrease over time by reducing dopamine levels during chronic treatment resulting in a loss of antipsychotic efficacy [5]. Therefore, the reasons for drug tolerance or treatment failure could lie in the reduced dopamine levels at dopaminergic synapses and the consequent lack of stimulation of the presynaptic D2R reserve. Furthermore, it has been proposed that restoration of initial synaptic dopamine levels may improve antipsychotic efficacy in chronic treatment, suggesting the blockade of dopamine transporter (DAT) as a therapeutic non-conventional option [5]. This evidence extends the canonical view of antipsychotics acting at postsynaptic receptors to the non-canonical action at the presynaptic dopaminergic terminal, either through inhibition of VGSCs or through the indirect stimulation of the D2 autoreceptor reserve. This insight may be relevant to elucidate the complex changes induced by antipsychotics within synapses but also shed light on DAT blockade as an additional treatment to revert antipsychotic treatment failure, such as in the TRS condition (Figure 2).

3.2. Dopaminergic Mechanisms and Correlations with Antipsychotics Receptor Profile: Insights from Present and Next Molecules

Antipsychotics have, with some exceptions (i.e., amisulpride and other benzamides), a complex receptor profile even if dopamine D2R occupancy or blockade is considered to be the necessary and possible sufficient mechanism of antipsychotic action. Exploring which and to what extent receptors that are part of an antipsychotic's profile are different from dopamine receptors could cooperate with the latter ones to help to unveil potential new antipsychotic mechanisms of non-canonical type.

3.2.1. Dopamine and Serotonin Receptors

The possibility that non-canonical mechanisms in dopaminergic signaling could intercept serotoninergic signaling has been recently challenged by the discovery of receptor dimers belonging to the different classes of neurotransmitters [82–84].

A trait that has been considered possibly critical for the atypicality of almost all new-generation antipsychotics is 5-HT_{2A} antagonism; specifically, a better affinity for 5-HT_{2A} over D2R, and thus a high 5-HT_{2A}/D2R ratio is considered a possible molecular predictor of atypicality, whose clinically and original definition is the low liability to elicit EPS [82]. In the framework of dopamine–serotonin receptor "cooperation" and with respect to the possible non-canonical dopaminergic MOA of antipsychotic drugs, an emergent role has been attributed to the 5-HT_{2A}/D2R dimers. Several preclinical in vitro and in vivo studies have identified dimerization of 5-HT_2 with D2R in rat striatum [82–84]. Specifically, it showed that stimulation of 5-HT_{2A}/D2R dimers with D2R agonists is antagonized by co-administration

of 5-HT_{2A}-agonists, suggesting a 5-HT_{2A}-mediated trans-inhibition of D2Rs, resulting in increased G_q compared with G_i signaling [85]. Furthermore, in vitro and in vivo studies have shown that 5-HT_{2A} can form dimers with metabotropic glutamate receptor 2 (mGluR2) [86,87]. In this context, 5-HT_{2A}/mGluR2 heterodimerization could potentiate mGluR2-G_i signaling and inhibit 5-HT_{2A}-G_q one [88]. In this context, serotonergic and glutamatergic drugs showed to bind the 5-HT_{2A}/mGluR2 heterocomplex, balancing G_i- and G_q-dependent signaling and eliciting antipsychotic action [88]. In addition, post-mortem studies in the cortex of untreated schizophrenia patients found higher expression of 5-HT_{2A} and lower expression of mGluR2, which might reflect a predisposing pattern to psychosis, indicating that the 5-HT_{2A}/mGluR2 complex might be involved in the altered cortical processes of schizophrenia resulting in a promising unconventional target for the treatment of psychosis [86]. Several lines of evidence indicated that 5-HT_3 is involved in the modulation of dopaminergic activity in mesolimbic and nigrostriatal pathways [89–91], suggesting the role of 5-HT_3 antagonists in mimicking the effects of antipsychotic drugs. Clinical evidence on single-marker and haplotype analyses among different mutations of serotonin receptor subtypes (*HTR2A*, *HTR3A*, and *HTR4*) in patients with TRS found that the daily dosage of neuroleptics received during maintenance therapy was significantly higher in patients with the T/T genotype of the *HTR3A* rs1062613 polymorphism, supporting the relationship between the *HTR3A* polymorphism and the potential development of TRS [92]. 5-HT_3 antagonism is yet to be clarified [93]; also 5-HT_6 antagonism was shown to attenuate the pro-psychotic effects of both MK-801 (also known as dizocilpine hydrogen maleate, a non-competitive antagonist at NMDAR) [94] and PCP in animal models of schizophrenia [95,96]. Furthermore, the selective 5-HT_7 receptor antagonist SB-269970 improves ketamine-induced attention and cognitive inflexibility, although its role has not yet been elucidated [97]. Partial 5-HT_{1A} agonists are known to have effects shared in part by 5-HT_{2A} antagonists in different biological systems [98] with anxiolytic and antidepressant efficacy [99,100]. Moreover, it has been suggested that 5-HT_{1A} agonism contributes to the atypical profile of antipsychotics [101], reducing movement disorders liability [102,103] and improving cognitive and affective symptoms [104,105]. In addition, association studies between genetic variants of the *HTR1A*, as well as solute carrier family 6, member 4 (*SLC6A4*) genes and clinical outcomes in schizophrenia, have shown that rs6295 and 5-HTTLPR polymorphisms significantly influence clinical symptoms in schizophrenia [106]. Finally, the involvement of $5HT_{1A}$ in schizophrenia pathophysiology is also confirmed by an in vitro preclinical study in PC12 cells treated with clozapine: it is demonstrated a decrease in tyrosine hydroxylase levels, with subsequent reduction in dopamine levels, probably mediated by D2R and $5HT_{1A}$ stimulation [107].

3.2.2. GABA Receptors

The main inhibitory neurotransmitter in the human central nervous system (CNS) is GABA. In postnatal development, GABAergic neurons are instrumental to the formation of brain circuits and are also involved in the pathophysiology of schizophrenia [108]. Animal models in which rat were treated with MK-801 exhibited a reduction in the density of parvalbumin-immunoreactive GABAergic neurons in the mPFC [109], partially resembling some findings of schizophrenia post-mortem brains [110]. Several abnormalities in GABA neurotransmission have been reported in patients with schizophrenia and TRS, such as morphological alterations in cortical and hippocampal GABA interneurons [108], reductions in cerebrospinal fluid (CSF) GABA levels in first-episode psychosis (FEP) [111], decreased glutamic acid decarboxylase (GAD67) levels in the dorsolateral PFC (DLPFC) [112,113], reduction in $GABA_B$ receptors expression in the post-mortem PFC and hippocampus [114,115], and genetic polymorphisms of *GAD67*, *GABBR1*, and *GABBR2* genes, which encode for the $GABA_B$ receptor [116]. An impaired ability to filter external auditory sensory information mediated by altered $GABA_B$ receptor firing has been associated with schizophrenia [117,118]. Specifically, an increase in the cortical silent period directly correlated with GABA function was observed in clozapine-treated patients compared to other antipsychotics [119,120], suggesting clozapine's ability to improve signal-to-noise discrimination [121], potentially through the potentiation of $GABA_B$-mediated

inhibitory transmission [119,122]. Through X-ray crystal structure analysis, a recent study demonstrated that clozapine binds directly to the $GABA_B$ similarly to baclofen, a $GABA_B$ receptor agonist proposed as a non-canonical antipsychotic [122]. Furthermore, a proton magnetic resonance imaging (^{1}H-MRS) study measured GABA levels in the midcingulate cortex (MCC) of TRS patients, stratifying them into clozapine-resistant schizophrenia (CRS) and TRS patients. The results showed higher GABA levels in CRS compared to TRS patients suggesting the potential implication of GABA to clozapine resistance [123]. Conversely, a recent meta-analysis reported overall decreased GABA levels in the MCC of FEP patients compared to healthy control (HC) and elevated levels of glutamate and glutamate + glutamine (Glx, glutamate neurotransmitter and its precursor) in the same region of TRS patients suggesting a disruption of the excitatory/inhibitory balance in schizophrenia spectrum disorders [124]. Abnormalities in Glx levels have been associated with schizophrenia, possibly contributing to the dysfunction of glutamatergic neurotransmission [125,126]. Glutamate is released into the synaptic cleft and binds glutamate receptors at the PSD. Specifically, glutamate is subsequently removed by astrocytes and converted to glutamine by glutamine synthetase [127]. Then, glutamine can be internalized into the presynaptic terminal and converted to glutamate by phosphate-activated glutaminase [128,129]. Intriguingly, Madeira and collaborators suggested that circulating Glx levels exhibit a biphasic pattern in schizophrenia, with an increased glutamine/glutamate ratio at the onset and decreased levels with the progression of the disease [130]. α5-GABAARs have been measured in the hippocampus by means of PET [11C]Ro15-4513, showing lower levels in first-episode schizophrenia patients antipsychotics naïve compared to controls, while no differences are found in patients on antipsychotic treatment compared with controls [131]. Beyond some indirect effects of antipsychotics on GABA neurotransmission, there was a long-standing acknowledgement that antipsychotics do not act directly at GABAergic receptors. This view has been challenged recently by the observation that applying in vivo fiber photometry and chemogenetics antipsychotics (i.e., olanzapine and clozapine) may directly bind and work as antagonist $GABA_A$ receptors in ventral tegmental area (VTA). As a consequence, GABA neurons are activated, and the GABAergic projection from VTA to the NAc is involved in such antipsychotic effects [132].

3.2.3. Noradrenergic Receptors

Alpha-adrenoceptor 1 (α_1) and alpha-adrenoceptor 2 (α_2) antagonism are both considered to be involved in modulating dopamine release in the PFC through firing dopaminergic neurons in the VTA [133], as demonstrated by the selective α_1 antagonist action of prazosin, which is responsible for enhancing the cognitive performance of MK-801 pretreated rats [134]. The available evidence indicates that blocking α_1 by antipsychotics may help to suppress positive symptoms, particularly in acute schizophrenia, whereas blocking α_2, a prominent effect of clozapine and, to a lesser extent, risperidone, may instead help to partially relieve negative and cognitive symptoms. While α_1 blockade may inhibit striatal hyperdopaminergia at the presynaptic level, α_2 blockade may enhance and improve dopaminergic function in PFC [133]. In fact, non-selective α_2 blockage has been linked to the effects of atypical antipsychotics such as clozapine and antidepressants such as mirtazapine. It has been suggested that α_{2C} and α_{2A} heteroreceptors can regulate non-noradrenergic transmission, such as serotoninergic and dopaminergic, by sharing autoreceptor functions to inhibit noradrenaline release via negative feedback. In addition, while α_{2A} seems to be highly distributed across the CNS, α_{2C} expression is less abundant, suggesting the differential modulation of regional neurotransmission. α_{2C} antagonism could be helpful during states of low endogenous noradrenergic activity, whereas α_{2A} antagonism could be significant during states of high noradrenergic tone. Specifically, preclinical studies have shown that the antagonism at the α_{2C} represents a non-canonical MOA for the regulation of GABA release in the striatum, inducing inhibition of GABA neurons projecting to cortical pyramidal neurons correlating with antidepressant/antipsychotic and procognitive-like effects [135,136]. In this context, α_{2C} antagonists could unconventionally mitigate schizophrenia-associated symptoms [136], ameliorating cognitive deficits and PCP-induced social interaction impairment [137–139].

Furthermore, it has been proposed that clozapine MOA at the α_1 and α_2 receptors could globally stabilize dopaminergic transmission [46]. In fact, its α_1 antagonism could affect positive symptoms by attenuating limbic hyperdopaminergia, whereas α_2 blockade could act on negative symptoms by increasing prefrontal dopaminergic activity, both contributing to improving secondary negative symptoms [140].

Preclinical studies have shown that the antipsychotic effect of risperidone can be potentiated by additional treatment with an α_2 antagonist, idazoxan, resulting in the attenuation of EPS and the enhancement of cortical dopamine release and NMDAR-mediated responses [141] (Figure 3). Consistent with these findings, the α_2 antagonism action of clozapine together with low D2R affinity could be considered a combined non-canonical MOA intercepting dopamine function and possibly relevant for its efficacy in TRS [141]. Moreover, the combination of idazoxan and raclopride, a selective D2R/D3R antagonist, was proposed to produce an atypical antipsychotic profile partially overlapping the clozapine MOA [142]. Nevertheless, the co-administration of raclopride and idazoxan was not able to reverse PPI deficit in rat animal model of schizophrenia, challenging the hypothesis that simple α_2/D2R blockade may elicit atypical antipsychotic activity [142]. Another attempt to combine a D2R antagonism with adrenoreceptor α_2 antagonism was the combination/augmentation of idazoxan with haloperidol [143] or fluphenazine [144], yielding mixed results. Overall, the combined dopamine D2R and adrenoreceptor α_2 antagonism could be a non-canonical dopaminergic strategy worth further exploration.

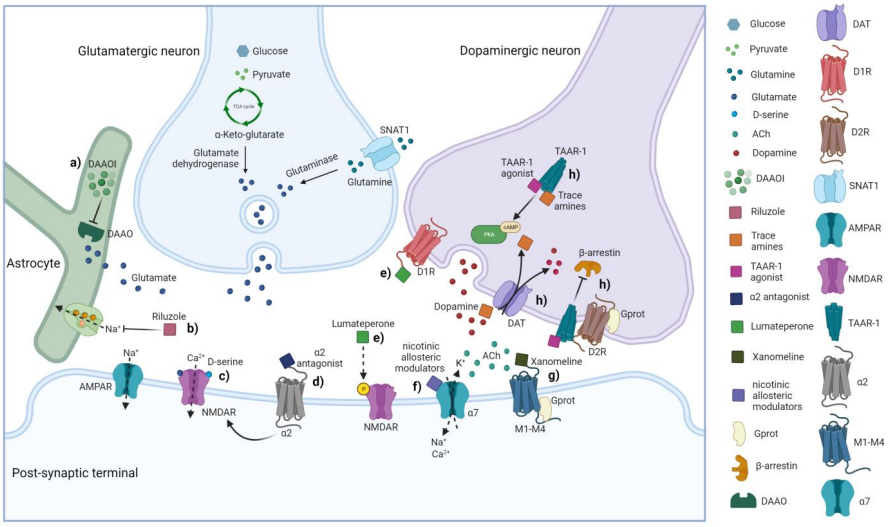

Figure 3. Mechanisms of action of molecules with non-canonical antipsychotic action: (**a**) DAAO inhibitors are capable of inhibiting the DAAO enzyme expressed by astrocytes; (**b**) riluzole reduces the synaptic release of glutamate by inhibiting voltage-gated sodium channels and calcium currents and increases astrocytic reuptake of glutamate enhancing cortical glutamate metabolism [145,146]; (**c**) D-serine acts as a co-agonist at synaptic NMDARs enhancing glutamatergic tone and its levels are reduced by DAAO activity, responsible for D-serine catabolism; (**d**) α2 antagonist enhances both cortical dopamine release and NMDAR-mediated responses; (**e**) lumateperone acts on dopaminergic D1R and D2R stimulating the phosphorylation of NMDAR subunits [147]; (**f**) α7 nicotinic positive allosteric modulators mitigate cognitive symptoms by eliciting acetylcholine release; (**g**) xanomeline is a central selective muscarinic agonist of M1 and M4 demonstrated to have antipsychotic properties despite being devoid of a direct effect on D2R [148]; (**h**) TAAR-1 agonists act on the intracellular TAAR1 receptors expressed by dopaminergic neurons and functionally related to receptors for biogenic amines. DAAO, D-amino acid oxidase; DAAOI, D-amino acid oxidase inhibitor; SNAT1, Sodium coupled neutral amino acid transporter 1; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NMDAR, N-methyl-D-aspartate receptor; D1R, Dopamine receptor D1; D2R, Dopamine receptor D2; cAMP, Cyclic adenosine monophosphate; PKA, Protein kinase A; TAAR-1, Trace amine-associated receptors 1; DAT, Dopamine transporter; P, phosphorylation; Ach, Acetylcholine; M1, Muscarinic receptor 1; M4, Muscarinic receptor 4; α2, α2 adrenoceptor; α7, α7 nicotinic receptor; Gprot, G protein; Na^+, Sodium; Ca^{2+}, Calcium; K^+, Potassium. Created with BioRender.com on 7 March 2023.

3.2.4. Muscarinic Receptors

The role of acetylcholine is crucial for hippocampal function, including learning and memory processes impaired in schizophrenia, supporting disturbances of cholinergic systems in such disease [149,150]. The excitatory postsynaptic muscarinic receptors 1 (M1) and muscarinic receptors 4 (M4) are the main cholinoceptive targets in the PFC and thus may be involved in both the pathology and pharmacotherapy of schizophrenia [151]. Clinical evidence has shown that subjects with schizophrenia show a selective reduction in the expression of muscarinic receptors (especially M1) in the CNS [149–152] associated with cognitive impairment. Since M1 are critical for PFC acetylcholine functions [151], it has been suggested that the reversal of M1 expression could be a potential therapeutic target for antipsychotics, as demonstrated in a preclinical study using clozapine metabolite, N- desmethylclozapine, that exhibit an antagonism at M1 [153–155]. Preclinical studies hypothesized that positive allosteric modulation of M1 could enhance glutamatergic transmission mediated by the NMDAR in the hippocampus [156]. Moreover, the administration of selective M1 agonists showed to improve long-term depression (LTD), cognitive functions, and social skills in schizophrenia mouse models [157], providing new insights into synaptic alterations that may contribute to behavioral deficits and supporting M1's role as an unconventional target for the treatment of schizophrenia. In contrast, the func-

tion of muscarinic receptor 3 (M3) has not been elucidated in the pathophysiology of schizophrenia other than probably related to the adverse effects of antipsychotics, such as type 2 diabetes [158], considering that M3 mediates insulin release from pancreatic β cells directly through G_q protein signaling [159] and indirectly through β-arrestin and polycystin 1 (PKD1) signaling [158]. Of interest, De Luca and collaborators have demonstrated that single-nucleotide polymorphisms (SNPs) of the muscarinic receptors 5 (*M5*) gene are associated with susceptibility to schizophrenia [160]. In addition, preclinical studies in mice with constitutive deletion of the *M5* gene have reported affected sensorimotor gating and PPI mechanisms [161]. Preclinical evidence has reported the involvement of M4 in cognitive functioning [162] and the prevention of hyperexcitability of midbrain dopaminergic neurons, presenting M4 agonists as an unconventional strategy for the treatment of disorders associated with hyperdopaminergia [163]. post-mortem studies in schizophrenia patients have reported low levels of M1, M2, and M4 in the striatum affecting motivation and motor control [152]. Indeed, M1–M4 agonism seems to be an interesting pharmacological mechanism for antipsychotics, as the dopamine-acetylcholine balance is relevant to decrease behavioral disturbances [164–166]. In this context, Shannon and coworkers demonstrated, in conditioned avoidance response, that muscarinic receptor agonists decreased the avoidance response in a manner similar to antipsychotics, suggesting that muscarinic receptor agonists may provide a non-canonical approach to the treatment of psychosis [164]. Thus, the muscarinic receptor agonist xanomeline demonstrated antipsychotic properties despite being devoid of a direct effect on D2R [148] but acting as a selective agonist of central muscarinic receptors M4 and M1 [167], proving significant efficacy in reducing positive and negative syndrome scale (PANSS) total score with associated peripheral side effects [152,168,169]. Radioligand binding studies on cloned human receptors confirmed that xanomeline has a substantial affinity for muscarinic receptors [167], as well as for 5-HT_1 and 5-HT_2 receptor subtypes [148]. Watson and coworkers have shown xanomeline to be a potent agonist of 5-HT_{1A} and 5-HT_{1B} receptors in native tissues and/or cloned cell lines and an antagonist of 5-HT_2 receptor subtypes [167], speculating potential antipsychotic activity related to action on these receptors. Despite the effect on M1 and M4 receptors is also shared by the atypical antipsychotic clozapine, Thomsen and coworkers inferred that the effects on PPI through both M1 and M4 in mice do not support the role of these receptors in mediating antipsychotic-like effects of clozapine [166]. The central and peripheral antimuscarinic affinity of antipsychotics is responsible for side effects, such as dizziness, drowsiness, confusion, blurred vision, and others [170,171]. The expedient for limiting peripheral cholinergic effects has been to co-administer xanomeline with trospium chloride, a peripheral muscarinic antagonist unable to cross the blood–brain barrier (BBB). Several muscarinic agonists have been shown to exert a functional antidopaminergic effect, particularly in the VTA, despite their lack of affinity for dopamine receptors [172]. A growing body of preclinical evidence has shown that xanomeline reverses sensory-motor gating deficits but may also improve cognitive dysfunction [173]. Clinical studies have tested the safety and efficacy of xanomeline and trospium as monotherapy in non-TRS patients [168], while the putative role in TRS may be inferred from the use of clozapine, whose metabolite norclozapine acts as an M1 and M4 agonist [46]; thus xanomeline's non-canonical MOA could be a valuable augmentation strategy to conventional antipsychotics in poorly responsive schizophrenia patients [169,174] (Figure 3).

Of interest, α*7* nicotinic receptors reduced levels associated with impaired auditory gating have been reported in the hippocampus of subjects with schizophrenia [175]. In particular, clozapine showed to dose-dependently normalize auditory gating in mice through α*7* nicotinic receptors, an effect not shared with haloperidol [176]. While subchronic administration of MK-801 reduced protein and gene expression of α*7* nicotinic receptors in the hippocampus, clozapine treatment restored α*7* expression and reversed cognitive deficits in male rats [177]. Although typical antipsychotics are associated with cigarette smoking in patients with schizophrenia, clozapine appears to reduce nicotine use [178–180], probably due to its peculiar action on nicotinic receptors.

Taking this evidence together, positive allosteric modulators of α7 nicotinic receptors have been proposed as an additional non-canonical strategy to mitigate cognitive symptoms in schizophrenia [177,181,182] (Figure 3). In phase II double-blind Randomized Clinical Trial (RCT), the agonist of the α7 receptor encenicline was tested on cognitive domains as an augmentation strategy and showed clinically significant improvements in schizophrenia patients [183]. Nicotinic agonists are thought to primarily affect cognitive symptoms [184], while muscarinic agonists have been shown to improve positive symptoms [185].

In summary, α7 nicotinic and M1/M4 agonists, as well as positive allosteric modulators in add-on/augmentation to dopamine D2R occupancy, could be considered among promising non-canonical strategies for schizophrenia treatment [168,169,183]. It remains to be understood which antipsychotic with which receptor profile should be considered the best fit for a such combination therapy.

3.2.5. Histamine Receptors

Histamine has a remarkable role as a regulator of several neurotransmitters and critical brain functions [186]. Approximately 64,000 histaminergic neurons in the human brain have their soma in the tuberomamillary nucleus in the posterior hypothalamus and send their axons to several brain areas, including the thalamus, hippocampus, striatum, amygdala, and cortex [186]. Histamine acts through at least four G-protein-coupled receptors (H1–H4), of which H1, H2, and H3 receptors are expressed in the CNS [187]. However, clinical experimental data on the role of histamine in psychosis are scarce, whereas preclinical evidence is challenging. Animal studies have shed on the potential role of histamine system and traditional models of psychosis, as well as interactions between histaminergic drugs and antipsychotics. Indeed, following the stimulation of the D2R, methamphetamine has been shown to increase histamine levels in rat brains, suggesting that blockade of the H3 attenuates the effect of amphetamines on locomotion [188], an effect replicated in *HRH3* (*H3 receptor gene*)-KO mice that exhibited decreased spontaneous locomotion and poorly respond to methamphetamine [189]. In this frame, Pillot and colleagues have suggested that endogenous histamine and dopamine cooperate to modulate the activity of striatal projection neurons fueling interest in the H3 antagonism as an unconventional antipsychotic strategy, possibly when combined with D2R occupancy [190]. While the antagonism of clozapine at the H3 might contribute to its overall clinical efficacy [191–194], H4 agonism seems to be related to severe adverse events, such as agranulocytosis [195]. In addition, both H3 and H4 may mediate multiple interactions between neurotransmitter systems involved in modulating appetite, satiety, and food intake relevant to clozapine's cardiometabolic side effects [196,197]. In vivo functional PET neuroimaging studies showed that schizophrenia patients had a lower binding affinity for the H1 in the frontal cortex, PFC, and cingulate gyrus compared with HC [198]. Furthermore, in post-mortem studies, H1 were reduced in the frontal cortex of chronic schizophrenia patients [199]. However, the binding of the antipsychotic clozapine, a potent H1 antagonist [71,200], is believed to be responsible for several side effects, including weight gain, sedation, and orthostatic hypotension [201–205]. In addition, it was found that the H1 antagonism of several antipsychotics could expose schizophrenia patients to the risk of ischemia [206]. H1 blockade could be implicated in the enhancement of sensorimotor plasticity and memory functions, suggesting that H1 antagonism may result in antipsychotic action [207]. A comparative in vitro and in vivo re-evaluation study showed that clozapine is a complete H2 inverse agonist and that its repeated administration increases H2 regulation in rat brain, suggesting that clozapine's histaminergic affinity might partially account for its atypical profile, as well as with that related to central and peripheral side effects [197].

Furthermore, a double-blind, parallel-group RCT study evaluated the potential beneficial effect of the H2 antagonist famotidine on negative symptoms in TRS patients, suggesting the novel pharmacological potential of H2 antagonism as a non-canonical strategy to treat negative symptoms in TRS [208].

3.2.6. TAAR1

Among non-canonical mechanisms intercepting dopaminergic signaling in treating schizophrenia, trace amines and their receptor have emerged strongly. Endogenous trace amines, which structurally resemble monoamines, such as serotonin and dopamine, activate the trace amine-associated receptor 1 (TAAR1) [209]. Since trace amines have been shown to alter the release and/or response to dopamine, norepinephrine, acetylcholine, and GABA [210], they are thought to be potential neuromodulators. When TAAR1 and D2R interact, a reduction in β-arrestin 2 recruitment is detected, silencing the GSK3 cascade via Akt [211,212]. Preclinical research suggests that TAAR1 agonists may improve not only the behaviors proxy of positive symptoms but the one mimicking negative and cognitive symptoms too, without causing motor disorders or weight gain [213]. In order to be considered a multimodal therapeutic target for neuropsychiatric diseases, the role of TAAR1 as a critical node in the regulation of dopaminergic signaling has been established through a combination of experimental preclinical and translational studies [212] (Figure 3). More attention will be paid to dopamine, glutamate, and serotonin regulation by TAAR1 as a non-canonical mechanism of antipsychotic efficacy [212]. SEP-363856, a novel therapy approved by the Food and Drug Administration for the treatment of schizophrenia, is a TAAR1 agonist in phase III clinical development. Since this compound modulates dopamine release without directly interacting with presynaptic and/or postsynaptic D2R, it may be able to treat TRS when other antipsychotics have failed and/or DSP has developed [174]. Specifically, SEP-363856 reduced the PANSS total score significantly more than the placebo and standard treatments in patients with acute schizophrenia [214], also improving the safety profile [215].

Furthermore, it should be noted that this molecule acts primarily at the presynaptic level, which is believed to be the pivotal site of dopaminergic dysregulation [174].

Consistent with these results and TAAR1 agonists' unique MOA, the beneficial effect of these compounds as non-canonical therapy for TRS can be assumed [174].

3.2.7. Dopamine-Antagonism and Glutamate-Based Augmentation of Antipsychotics

There is an emerging interest in dissecting non-canonical mechanisms that point to glutamate involvement as an antipsychotic augmentation strategy. The NMDAR hypofunction hypothesis predicts a reduced function of parvalbumin-positive fast-spiking GABA interneurons considered a major determinant of schizophrenia molecular pathophysiology with a possible role in poor response to antipsychotics acting at D2R [216]. NMDAR function can be improved by increasing D-amino acids by D-amino acid oxidase inhibitor (DAAOI), sodium benzoate, which is used as a therapy to target residual positive symptoms and TRS [210].

Encouraging clinical studies have shown that the strategy of clozapine augmentation with sodium benzoate, which is expected to promote the activation of NMDAR, exhibits beneficial effects overall in patients with CRS [217] and improves cognitive functions in patients with chronic schizophrenia [218]. Further research is needed to understand whether sodium benzoate, as an add-on to clozapine, can support efficacy, tolerability, and potential unconventional use for TRS and CRS [217]. Some evidence suggests low bioavailability and poor capability across the BBB, limiting the use of DAAOIs [219]. The efficacy results are promising, and sodium benzoate may be an unconventional option for difficult-to-treat patients, but pharmacokinetic issues need to be better addressed.

Modulators of glutamatergic neurotransmission have been tested in several studies in combination with clozapine. However, no cumulative evidence of significant clinically beneficial differences was shown, except for improvement in negative symptoms with memantine and minocycline [220]. It is possible that the use of additional glutamatergic agents in patients receiving clozapine may have little effect, possibly due to a putative ceiling effect on the NMDAR transmission enhancement already exerted by clozapine [221]. Strategies based on the potentiation of glutamatergic signaling by glycinergic agents (e.g., glycine and D-serine), glycine transporter 1 (GlyT1) inhibitors (e.g., bitopertin and BI 425809), and other glutamate allosteric NMDAR modulators (e.g., CNS4) have been tested. D-serine has been assessed in several RCTs in augmentation to clozapine or other

antipsychotics, showing poor beneficial effects among patients treated with clozapine, whereas a meta-analytic study indicated that adjunctive treatment with D-serine and glycine was effective with other antipsychotics in improving the negative symptoms of schizophrenia [222] (Figure 3). A preclinical in vivo electrophysiological study reported the changes in endogenous concentration of brain kynurenic acid (KYNA) used to analyze the interaction between clozapine and the glycine site of NMDAR. KYNA is an endogenous blocker of α7 nicotinic receptors and a glutamate-receptor antagonist, preferentially blocking NMDAR. The results showed that the endogenous levels of brain KYNA were crucial for the response to clozapine on the VTA dopamine neurons, suggesting the ability of clozapine to interact with glutamatergic mechanisms via NMDA/glycine receptors [223].

An increase in glycine availability may also be obtained by administering GlyT1 inhibitors, which have proven to modulate both glutamatergic and dopaminergic neurotransmission in an animal model of schizophrenia [224]. Bitopertin showed no significant effects on overall symptoms in schizophrenia patients [225]. Encouraging evidence indicates the putative efficacy of another non-sarcosine GlyT-1 inhibitor, BI 425809, recently evaluated in a 12-week, double-blind, phase II RCT study associated with cognitive improvement in schizophrenia patients [226].

Experimental strategies to add D-amino acids to antipsychotic drugs to enhance response to treatment in schizophrenia have been investigated for several years, but despite a sufficiently strong rationale and translational background [221], it is still missing to take advantage of the availability of D-amino acids used in the clinical setting.

Fluctuations in synaptic glutamate homeostasis led to aberrant activity of NMDARs, which are involved in the pathogenesis of neuropsychiatric disorders, suggesting the clinical relevance of allosteric modulators at this site. A recent preclinical study characterized an allosteric modulator, CNS4, which is responsible for enhancing the currents of NMDARs dependent on the concentration of endogenous glutamate [227]. CNS4 showed to alter the potentiation of glutamate in rat cortical, striatal, and cerebellar neurons by enhancing ions influx through native NMDAR activity, representing an unconventional candidate for TRS [227].

A further non-canonical treatment approach for schizophrenia is represented by riluzole, a drug used for amyotrophic lateral sclerosis that reduces the synaptic release of glutamate by inhibiting VGSCs and calcium currents [145,146]. Preclinical studies have also shown other mechanisms of riluzole that potentially impact glutamatergic dysfunction in schizophrenia: (i) increase in the astrocytic reuptake of glutamate [228]; (ii) neuroprotective effect via the upregulation of glutamate transporter 1 (GLT-1) in a voltage-sensitive ion channels blockade independent manner [229]; (iii) improved cortical glutamate cycling [230]; and (iv) reducing the size of the releasable presynaptic glutamate, inhibiting protein kinase C (PKC)-dependent Munc18-1 phosphorylation [231] (Figure 3). A recent functional magnetic resonance imaging (fMRI) study measuring resting anterior cingulate cortex (ACC)-functional connectivity examined the ability of riluzole to modulate glutamate metabolite levels and functional cortical connectivity, proposing its role in normalizing Glx levels and increasing cortical connectivity in TRS patients [232]. These results also indicated that glutamatergic function and cortical connectivity were linked to the cognitive symptoms in TRS and thus pharmacologically modulated [232]. An RCT study with 50 chronic schizophrenia patients showed that riluzole significantly reduced the severity of negative symptoms compared to the HC group [233]. In this context, riluzole might have a beneficial effect on glutamatergic excitotoxicity based on the spatiotemporal boundaries of NMDAR hypofunction [234]. It has been hypothesized that NMDAR hypofunction occurs initially during the maturation of GABAergic neurons, causing reduction in intrinsic excitability and GABA release and disinhibition of pyramidal neurons. Cortical disinhibition, in turn, could lead to increased glutamate spillover and subsequent homeostatic dysregulation of NMDAR function in pyramidal neurons. These two temporally distinct and complementary hypotheses of NMDAR hypofunction could together explain the complexity of the trajectory of schizophrenia's pathophysiology [234].

Corbett and co-workers proposed that the antipsychotics clozapine and olanzapine may antagonize dopamine-induced and non-competitive NMDAR-associated behaviors [235].

Preclinical in vivo studies have shown that antipsychotics antagonize the mouse climb test and the locomotion and fall test in a dose-dependent fashion [235]. Non-competitive NMDAR antagonists, such as PCP and MK-801, can induce social withdrawal, locomotion and falling behavior in rodents that are selectively reversed by clozapine and olanzapine, albeit not as a direct result of blocking D1Rs or D2Rs. These results suggested that the mechanisms underlying non-competitive NMDAR antagonism may be explored to select novel non-canonical drugs for schizophrenia-negative symptoms and TRS [235].

3.3. Dopamine Antagonism and Trans-Synaptic Effects at the Postsynaptic Density

The postsynaptic density (PSD) is a macromolecular complex located at the postsynaptic terminals of glutamatergic synapses, detectable with electron microscopy as a disc with a surface area of approximately 0.07 μm^2 and a thickness of 30–40 nm [236–239]. The PSD is composed of over 2100 proteins [240] organized in multiple orders of stratified molecules, including the following: receptors, i.e., NMDAR, AMPAR, mGluR type I, Kainate receptor; adaptors/scaffolds, i.e., Postsynaptic density protein 95 (PSD-95), Disrupted in schizophrenia 1 (DISC1), Stargazing, Homer, SH3 and multiple ankyrin repeat domains (Shank); cytoskeleton proteins (i.e., Tubulin, Actin, α-internexin); and enzymes [241,242]. NMDAR is the crucial structure of the PSD, representing the core of the PSD molecular machinery [243]. Pathological conditions not only modulate subunit composition, as demonstrated in a preclinical study in a PCP mice model that showed an increase in NR2A and NR2B NMDAR subunits [244] but also the complete composition of the PSD, resulting in morphological and functional modifications (e.g., spine loss in the auditory cortex in schizophrenia patients) [245,246]. Alterations in glutamate neurotransmission are also attributable to presynaptic terminals modifications in both vesicular glutamate transporters (VGLUT), whose transcript is increased through two common SNPs detected in schizophrenia patients [247], and several proteins related to glutamate release, which are reduced in the ACC of schizophrenia patients [248]. These findings are in opposition when compared with observations in TRS patients that exhibit an increase in glutamate and glutamate metabolites levels in dorsalACC evaluated by 3T-^{1}H-MRS or fMRI [232,249].

This complex molecular arrangement may act as a spatio-temporal organizer with multiple converging signaling possibly exiting in the structural changes of synaptic plasticity processes [250,251]. Considering the crucial role of these events in the pathophysiology of psychiatric disorders, including schizophrenia, it is not surprising that alterations in the expression or structure of these constitutive proteins result in aberrant synaptic processes as reported by multiple evidence of several studies such as genome-wide association study (GWAS), post-mortem studies, proteomic analysis, and preclinical modeling that emphasize the relevant role of PSD structure in the intricate scenario of the genetic architecture and pathophysiology of schizophrenia and TRS [251–265]. Growing evidence points not only to functional alterations associated with genetic and structural changes in PSD proteins but also to the possibility of aberrant spatio-temporal and region- and cell-dependent modulations of specific domains in their structure, resulting in dysfunction that could underlie the psychopathology of the disease [266–269].

3.4. Antipsychotics and PSD Modulation: A Relevant Non-Canonical Antipsychotic-Induced Effect?

Consistent with the position of PSD in the mechanisms involved in synaptic plasticity, several studies have demonstrated the centrality of this structure in the effect of antipsychotic drugs and the role of dopamine occupancy [270–274]. Here, we report the effects of different antipsychotics on the most abundant PSD proteins.

3.4.1. Homer Proteins and Splicing Variants

Homer is a family of proteins located at the PSD associated with schizophrenia, as demonstrated by genetic clinical and preclinical studies investigating the *Homer1* gene [254,275,276]. This gene originates from two different types of molecules: the constitutive isoforms (Homer1b/c) and the inducible transcripts (Homer1a—Ania3) [277,278]. *Homer1a* is an imme-

diate early gene (IEG), and it can be induced by dopaminergic and glutamatergic manipulations [279,280]. It acts as a "dominant negative" for the constitutive form, reducing the formation of the tetrameric structures formed by Homer1b, thus triggering direct changes in PSD architecture and signaling [278,281,282].

Several preclinical studies have investigated the effects of antipsychotics and other drugs in the modulation of Homer1a and Homer1b/c by evaluating the involvement of different receptor profiles, particularly based on D2R occupancy and the timing of administration in the variable induction of these molecules, and thus in the different modes of synapse restructuring (Figure 4 and Table 1). Considering the effect of haloperidol and ziprasidone at D2R different from clozapine, it was found that acute haloperidol administrations, at low (0.25 mg/kg), medium (0.5 mg/kg), and high (0.8 mg/kg) doses are responsible for an increase in Homer1a transcript levels, as well as for Ania-3 splice variant for haloperidol 0.8 mg/kg [283], in the striatum as well as ziprasidone at low (4 mg/kg) and high (10 mg/kg) doses [283–299] (Table 1). Chronic administration and sacrifice after 90′ from the last injection of haloperidol at 0.8 mg/kg and 0.25 mg/kg, but not at 0.5 mg/kg, as well as ziprasidone at 10 mg/kg, are responsible for an increase in Homer1a levels in the striatum [283,284,286,287,300]. These findings suggest that Homer1a retains its qualitative and quantitative properties even after prolonged treatments, leading to the hypothesis that it does not encounter tolerance or desensitization phenomena as observed for other IEGs, such as *c-Fos* [301,302]. On the other hand, clozapine at 15 mg/kg and ziprasidone at 10 mg/kg are responsible for increased Homer1a levels in the cortex compared to haloperidol, which causes a decrease in the same brain region after both acute and chronic administration with a reduction of neuronal activity [286,289,292,296,300] (Table 1), probably not mediated by D2R transmission but due to their remarkable serotoninergic action [284]. Chronic asenapine administration is responsible for reducing Homer1a levels in the insular cortex [300], whereas acute administration at low (0.05 mg/kg) and medium (0.1 mg/kg) doses are responsible for an increase in Homer1a levels in both cortical and subcortical regions [288]. This effect is probably related to the progressive stimulation of dopamine, noradrenaline, and serotonin efflux in PFC and NAc, strictly dependent on both $5HT_{2A}$ and α_2 blockade caused by asenapine [303] (Table 1). Asenapine and haloperidol chronic administration significantly shifted the Homer1a/Homer1b/c ratio toward Homer1b expression in cortical regions and toward Homer1a in subcortical regions with different values depending on the doses of antipsychotics. These findings suggest that the variable spatial expression pattern of both Homer's constitutive and inducible forms may exert a differential impact on postsynaptic plasticity based on their opposite actions [288,300,304]. An increase in the striatum Homer1a levels is also detected after risperidone (3 mg/kg) and olanzapine (2.5 mg/kg) acute administration compared to sulpride, although the increase in the same levels after the administration of haloperidol at 0.8 mg/kg is greater probably related to the different affinity for D2R [305] (Table 1). Intriguingly, at the topographical evaluation, the signal of Homer1a after haloperidol, risperidone and olanzapine follows a dorsolateral–ventromedial gradient in the striatum [290].

The same distribution is followed by medium-sized spiny neurons, which are the striatal cells prominently expressing Homer1a induced by antipsychotics [306,307] that could be related to the graded organization of the caudate–putamen [290] and with a different dorsal-to-ventral distribution of D1R and D2R [308–311].

In conclusion, antipsychotics may progressively recruit IEGs expression in cortical and subcortical regions based on their different timing and doses of administration, reflecting that a fine-tuned dose-dependent modulation of PSD proteins also depends on receptor occupancy at different doses underlying clinical efficacy, response, and side effects relevant to schizophrenia treatment response and resistance.

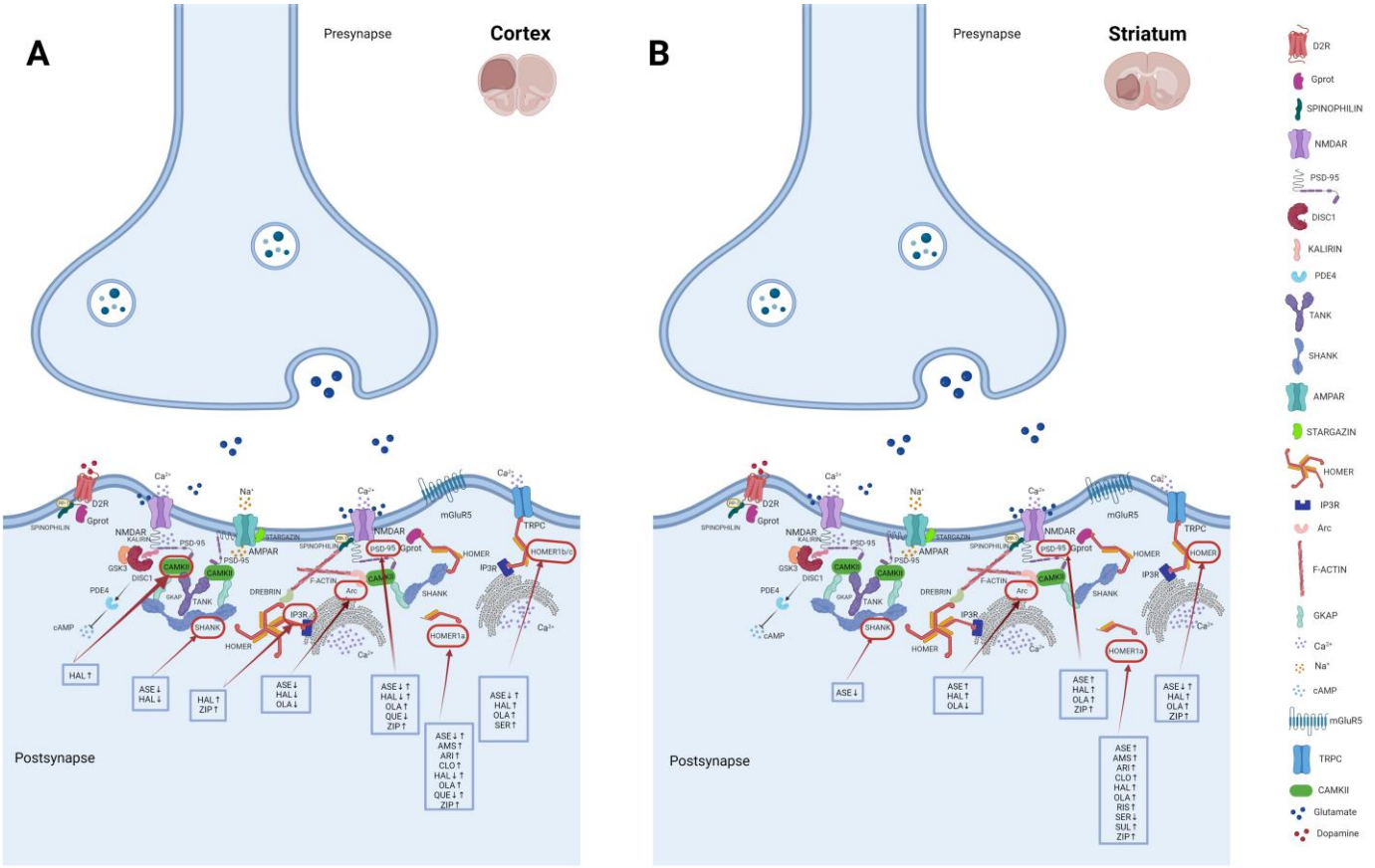

Figure 4. Antipsychotics and PSD modulation as relevant unconventional antipsychotic action. Panel (**A**). Modulation of PSD proteins by antipsychotics in rat cortical regions. Panel (**B**). Modulation of PSD proteins by antipsychotics in rat striatal regions. AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CAMKII = Calcium–calmodulin (CaM)-dependent protein kinase II; F-ACTIN = Filamentous actin; GKAP = guanylate kinase-associated protein; GSK3 = Glycogen Synthase Kinase 3 Beta; IP3R = IP3 (inositol 1,4,5-trisphosphate) receptor; mGluR5 = metabotropic glutamate receptor 5; NMDAR = N-Methyl-D-aspartic acid receptor; SHANK = SH3 and multiple ankyrin repeat domains; TANK = TRAF Family Member Associated NFKB Activator; PP-1 = protein phosphatase 1; D2R = dopamine receptor D2; Gprot = G protein; cAMP = cyclic adenosine monophosphate; AKT = protein kinase B; PKC = protein-chinasi C; GSK3 = glycogen synthase kinase-3; Ca^{2+} = calcium ion; DISC1 = disrupted-in-schizophrenia 1; PDE4 = phosphodiesterase 4A; Na^{+} = sodium ion; TRPC = transient receptor potential cation channel; PSD-95 = Postsynaptic density protein-95 kDa; HAL = haloperidol; CLO = clozapine; RIS = risperidone; OLA = olanzapine; SER = sertindole; ZIP = ziprasidone; APZ = aripiprazole; AMS = amisulpride; SUL = sulpride; ASE = asenapine. Created with BioRender.com on 7 March 2023.

Table 1. Modulation of PSD proteins' transcripts in different rat brain regions by antipsychotics and other psychotropic molecules related to their receptor profiles based on Sykes and co-authors' studies [312,313]. ↑ = increased levels; ↓ = decreased levels; M1 = primary motor cortex; M2 = supplementary motor cortex; IC = insular cortex; DMCP = dorsomedial caudate-putame; DLCP = dorsolateral caudate-putament; VMCP = ventromedial caudate-putamen; VLCP = ventrolateral caudate-putamen; ACC = anterior cingulate cortex; MC = motor cortex; SS = somatosensory cortex; AC = Auditory Cortex; FC = frontal cortex; DG = dentate gyrus; SNc = substantia nigra pars compacta, VTA = ventral tegmental area; MAC = Medial Agranular Cortex; Cab = Core of the nucleus accumbens; Sab = shell of the nucleus accumbens 5HT = serotonin; PSD = postsynaptic density; IP3R = Inositol 1,4,5-trisphosphate receptor; Arc = activity-regulated cytoskeleton-associated protein; mGluR5 = metabotropic glutamate receptor 5; αCaMKII = alpha-Ca^{2+}/calmodulin-dependent protein kinase-II; Shank = multiple ankyrin repeat domains; DAT = Dopamine Transporter; ERK = Extracellular signal-regulated kinases.

Gene	Drug	D2/5HT$_{2A}$ Affinity Ratio	Dose	Duration	Effects on Gene Expression/Rat Brain Region	Brain Region of Interest	Reference
Homer 1a	Haloperidol	0.00087	0.8 mg/kg	Acute treatment	↑ in striatum	DMCP, DLCP, VMCP, VLCP, CAb, SAb	[283,284,286–289,291–299]
					↓ in cortex	ACC, MAC, MC, SS, IC	[286,289,292,296]
				Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum and cortex	DMCP, DLCP, VMCP, VLCP, CAb SAb, ACC, MAC, MC, SS, IC	[283,284,286,287,300]
					↓ in cortex	MAC, MC, IC	[300]
				Chronic treatment (sacrifice after 24 h from last injection)	↑ in cortex	ACC, MAC, MC, SS, IC	[284]
			0.25 mg/kg	Acute treatment	↑ in striatum	DMCP, DLCP, VLCP	[288]
				Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum	DLCP, VLCP, DMCP, SAb	[300]
			0.5 mg/kg	Acute treatment	↑ in striatum	DMCP, DLCP, VMCP, VLCP	[288]
				Chronic treatment (sacrifice after 90′ from last injection)	↓ in cortex	MC	[300]
	Haloperidol + Valproate		0.8 mg/kg + 500 mg/kg	Acute treatment	↑ in striatum	DMCP, DLCP, VMCP, VLCP, CAb	[289]
	Ziprasidone	2.57	4 mg/kg	Acute treatment	↑ in striatum	DMCP, DLCP, VMCP, VLCP	
			10 mg/kg	Acute treatment	↑ in cortex and striatum	DMCP, DLCP, VMCP, VLCP, CAb, SAb, ACC, MC, SS, IC	[284]
				Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum	DLCP, VLCP, CAb SAb	
	Asenapine	3.39	0.05 mg/kg	Acute treatment	↑ in striatum and cortex	AC, M2, M1, SS, DMCP, DLCP, VMCP, VLCP, CAb	[288]
				Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum	DLCP	[300]
			0.1 mg/kg	Acute treatment	↑ in striatum and cortex	AC, M2, M1, SS, IC, DMCP, DLCP, VMCP, VLCP, CAb, SAb	[288]
				Chronic treatment (sacrifice after 90′ from last injection)	↓ in cortex	IC	[300]
			0.3 mg/kg	Acute treatment	↑ in striatum	DMCP, DLCP, VMCP, VLCP, CAb, SAb	[288]
	Olanzapine	1.00	2.5 mg/kg	Acute treatment	↑ in striatum and cortex	AC, M2, M1, I, DMCP, DLCP, VMCP, VLCP, CAb, SAb	[288,290]
				Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum	DLCP, SAb	[286,300]
	Sertindole	5.37	2 mg/kg	Acute treatment	↓ in striatum	SS, IC	
					↑ in cortex	SS	[283]
	GBR 12909	-	15 mg/kg	Acute treatment	↑ in striatum and cortex	FC outer, FC inner, Cingulate cortex, DLCP, VMCP, VLCP, CAb, Sab	[287]
				Chronic treatment (sacrifice after 90′ from last injection)	↑ in cortex	SS	[283]
	Aripiprazole	0.0093	12 mg/kg	Acute treatment	↑ in striatum	DMCP, DLCP, VMCP, VLCP	[287]
				Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum and cortex	FC inner, Cingulate cortex, DLCP,	
			30 mg/kg	Acute treatment	↑ in cortex	FC outer, FC inner, Cingulate cortex, SAb	[287]
	Clozapine	2.63	15 mg/kg	Acute treatment	↑ in cortex	ACC, MAC, SS, IC	[284]
					↑ in striatum	SAb	[287]
				Chronic treatment (sacrifice after 90′ from last injection)	↑ in cortex	FC inner, PC inner	
	Risperidone	1.62	3 mg/kg	Acute treatment	↑ in striatum	DLCP, VLCP	[290]
	Sulpiride	-	50 mg/kg	Acute treatment	↑ in striatum	VLCP, CAb	[290]
	Ketamine	-	25 mg/kg	Acute treatment	↑ in cortex	IC	[314]
	GBR-12909	-	30 mg/kg	Acute treatment	↑ in striatum	VMCP, SAb	[292]
	Caffeine	-	40 mg/kg	Acute treatment	↑ in striatum	DMCP, SAb	[292]
	Caffeine +. Haloperidol	-	40 mg/kg + 0.8 mg/kg	Acute treatment	↓ in striatum	DMCP, VMCP	[292]
	Nicotine + Haloperidol	-	1.5 mg/kg+ 0.8 mg/kg	Acute treatment	↑ in striatum	DMCP, CAb, SAb	[292]
	Escitalopram	-	12 mg/kg	Acute treatment	↑ in cortex	outer parietal cortex	[293]
	Citalopram	-	14 mg/kg	Acute treatment	↓ in cortex	M1, SS, IC	[289]
	Haloperidol + Escitalopram	-	0.8 mg/kg + 12 mg/kg	Acute treatment	↑ in striatum and cortex	outer parietal cortex, DLCP, VLCP, CAb	[293]
	Haloperidol + Citalopram	-	0.8 mg/kg + 14 mg/kg	Acute treatment	↑ in striatum and cortex	outer parietal cortex, DLCP, VLCP, DMCP, VMCP, CAb	[293]
	Amisulpride	0.00078	35 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum and cortex	VMCP, DMCP, ACC, MAC, MC, SS, IC	[295]
				Acute treatment	↑ in striatum	VMCP, DMCP	[298]
	Ketamine	-	50 mg/kg	Acute treatment	↑ in striatum	VMCP, VLCP	[315]
	Ketamine	-	12 mg/kg	Acute treatment	↑ in striatum	CAb, SAb	[315]
	SCH-23390	-	0.5 mg/kg	Acute treatment	↑ in striatum and cortex	VLCP, CAb, SAb, MAC, MC	[296]
	L-741,626	-	2 mg/kg	Acute treatment	↑ in striatum and cortex	VMCP, DMCP, VLCP, DLCP, CAb, SAb, MAC, MC	[296]
	U-99194	-	5 mg/kg	Acute treatment	↑ in cortex	MAC, MC	[296]
	Terguride	-	0.5 mg/kg	Acute treatment	↑ in striatum	VLCP, DLCP	[296]
					↓ in cortex	MC	
	Quetiapine	0.35	30 mg/kg	Acute treatment	↑ in cortex	ACC, M2, M1	[289]
				Chronic treatment (sacrifice after 90′ from last injection)	↓ in cortex	M2, M1, SS	
			15 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↓ in cortex	M2, M1, SS	
	Haloperidol + Mynocycline	-	0.8 mg/kg + 45 mg/kg	Acute treatment	↑ in striatum	VMCP, DMCP, DLCP	[299]

Table 1. *Cont.*

Gene	Drug	$D2/5HT_{2A}$ Affinity Ratio	Dose	Duration	Effects on Gene Expression/Rat Brain Region	Brain Region of Interest	Reference
Homer 1b/c	Ziprasidone	2.57	10 mg/kg	Chronic treatment (sacrifice after 24 h from last injection)	↑ in striatum	DLCP	[284]
			0.25 mg/kg		↑ in striatum	CAb	
	Haloperidol	0.00087	0.5 mg/kg	Acute treatment	↑ in striatum and cortex	M1, CAb	[288]
			0.8 mg/kg		↑ in striatum and cortex	AC, M2, M1, CAb	
			0.8 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum and cortex	DLCP, VMCP, VLCP, CAb, Sab, ACC, MAC, SS, IC	[286]
					↓ in striatum and cortex	VMCP, DMCP, MAC	[300]
	Asenapine	3.39	0.1 mg/kg	Acute treatment	↑ in striatum and cortex	AC, M2, M1, CAb	[288]
			0.3 mg/kg				
	Olanzapine	1.00	2.5 mg/kg	Acute treatment	↑ in striatum and cortex	AC, M2, M1, CAb	
	Sertindole	5.37	2 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↑ in cortex	ACC, MAC, SS, IC	[286]
	Ketamine	-	25 mg/kg	Acute treatment	↓ in cortex	MC	
	Ketamine	-	50 mg/kg	Acute treatment	↓ in striatum and cortex	MAC, MC, DLCP	[314]
	GBR-12909	-	30 mg/kg	Acute treatment	↑ in striatum and cortex	ACC, MAC, MC, SS, IC, VMCP, DMCP, DLCP	[292]
	Nicotine	-	1.5 mg/kg	Acute treatment	↑ in striatum and cortex	MAC, SS, DMCP, VMCP, CAb, SAb	[292]
	Caffeine +. Haloperidol	-	40 mg/kg + 0.8 mg/kg	Acute treatment	↑ in striatum	MAC, SS	[292]
	Nicotine + Haloperidol	-	1.5 mg/kg + 0.8 mg/kg	Acute treatment	↑ in striatum	ACC, MAC, MC, SS, IC, VMCP, DMCP, DLCP, CAb, SAb	[292]
	SCH-23390	-	0.5 mg/kg	Acute treatment	↑ in striatum	CAb	[296]
					↓ in cortex	MC	
	L-741,626	-	2 mg/kg	Acute treatment	↓ in striatum and cortex	VLCP, SAb, MC, SS, IC	[296]
	L-745,870	-	3 mg/kg	Acute treatment	↓ in striatum and cortex	VMCP, VLCP, SAb, MC, SS	[296]
	Terguride	-	0.5 mg/kg	Acute treatment	↓ in striatum and cortex	VMCP, VLCP, CAb, SAb, MC, SS, IC	[296]
PSD-95	Ziprasidone	2.57	10 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum	DMCP, DLCP, VMCP, VLCP, CAb, SAb	[284]
				Chronic treatment (sacrifice after 24 h from last injection)	↑ in striatum and cortex	VMCP, ACC, MAC, MC	
			0.25 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↓ in cortex	ACC, MAC, MC, SS, IC	[300]
	Haloperidol	0.00087	0.5 mg/kg	Acute treatment	↑ in cortex	AC, M1	[288]
					↑ in striatum and cortex	ACC, M2, M1, I, DMCP, DLCP, VMCP, CAb, SAb	
			0.8 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum and cortex	DMCP, DLCP, VMCP, VLCP, CAb, SAb, ACC, MC, SS	[284,286]
					↓ in cortex	ACC, MAC, MC, SS	[300]
				Chronic treatment (sacrifice after 24 h from last injection)	↑ in cortex	ACC, MAC, MC	[284]
	Asenapine	3.39	0.05 mg/kg	Acute treatment	↑ in striatum and cortex	AC, M2, M1, SS, I, DMCP, DLCP, VMCP, VLCP, CAb, SAb	[288]
			0.1 mg/kg	Acute treatment	↑ in striatum and cortex	AC, M2, M1, SS, I, DMCP, DLCP, VMCP, VLCP, CAb, SAb	[288]
				Chronic treatment (sacrifice after 90′ from last injection)	↓ in cortex	ACC, MAC, MC, SS, IC	[300]
			0.3 mg/kg	Acute treatment	↑ in striatum and cortex	ACC, M2, M1, SS, I, DMCP, DLCP, VMCP, VLCP, CAb, SAb	[288]
	Olanzapine	1.00	2.5 mg/kg	Acute treatment	↑ in striatum and cortex	ACC, M2, M1, SS, I, DMCP, DLCP, VMCP, VLCP, CAb, SAb	[288]
	Ketamine	-	25 mg/kg	Acute treatment	↓ in striatum	VMCP	[314]
	Ketamine	-	50 mg/kg	Acute treatment	↓ in striatum	VMCP	[314]
	MK-801	-	0.8 mg/kg	Acute treatment	↓ in striatum	VMCP, VLCP	[314]
	Haloperidol + Valproate	-	0.8 mg/kg + 500 mg/kg	Acute treatment	↑ in striatum and cortex	ACC, SS, DMCP	[289]
	Quetiapine	0.35	15 mg/kg	Acute treatment	↓ in cortex	M2, M1	[289]
	Citalopram	-	14 mg/kg	Acute treatment	↑ in striatum and cortex	ACC, M2, SS, IC, DMCP, DLCP, VMCP, VLCP, CAb, SAb	[289]
IP3R	Haloperidol	0.00087	0.8 mg/kg	Chronic treatment (sacrifice after 24 h from last injection)	↑ in cortex	MAC	[284]
	Ziprasidone	2.57	10 mg/kg				
Arc	Haloperidol	0.00087	0.25 mg/kg	Acute treatment	↓ in cortex	M2, M1, SS, I	[288]
				Chronic treatment (sacrifice after 90′ from last injection)	↓ in cortex	ACC, MAC, MC, SS, IC	[300]
			0.5 mg/kg	Acute treatment	↑ in striatum	DLCP, VLCP, CAb, SAb	[286]
				Chronic treatment (sacrifice after 90′ from last injection)	↓ in cortex	ACC; MAC, MC, SS	[300]
			0.8 mg/kg	Acute treatment	↑ in striatum	DMCP, VMCP, DLCP, VLCP, CAb, SAb	[286,298,299]
					↓ in cortex	AC, M2, SS	[286]
				Chronic treatment (sacrifice after 90′ from last injection)	↓ in cortex	ACC; MAC, MC, SS	[300]
	Asenapine	3.39	0.1 mg/kg	Acute treatment	↓ in cortex	AC, M2, M1	[288]
				Chronic treatment (sacrifice after 90′ from last injection)	↓ in cortex	MC, SS, IC	[300]
			0.3 mg/kg	Acute treatment	↑ in striatum	DLCP, VLCP, CAb	[288]
				Chronic treatment (sacrifice after 90′ from last injection)	↓ in cortex and stritum	MAC, MC, SS, IC, VMCP	[300]
			0.05 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum	DLCP	[300]
	Ketamine	-	25 mg/kg	Acute treatment	↑ in cortex	MAC, MC, SS, IC	[314]
	Ketamine	-	50 mg/kg	Acute treatment	↑ in cortex	ACC, MAC, MC, SS, IC, CAb, SAb	[314]
	Memantine	-	5 mg/kg	Acute treatment	↑ in cortex	MAC	[314]
	MK-801	-	0.8 mg/kg	Acute treatment	↑ in cortex	ACC, SS, CAb, SAb	[314]
	Caffeine	-	40 mg/kg	Acute treatment	↓ in cortex and striatum	IC, DMCP, VMCP, VLCP, CAb	[292]
	Nicotine	-	1.5 mg/kg	Acute treatment	↓ in cortex and striatum	MC, IC, VMCP	[292]
	GBR-12909	-	30 mg/kg	Acute treatment	↑ in striatum	CAb	[292]
	Caffeine	-	40 mg/kg	Acute treatment	↓ in striatum	IC, DMCP, VMCP, VLCP, CAb	[292]
	Caffeine +. Haloperidol	-	40 mg/kg + 0.8 mg/kg	Acute treatment	↓ in cortex and striatum	MC, SS, IC, VMCP, CAb	[292]
	Nicotine + Haloperidol	-	1.5 mg/kg + 0.8 mg/kg	Acute treatment	↑ in striatum	DMCP, CAb	[292]
	Olanzapine	1.00	2.5 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↓ in cortex and striatum	ACC, MAC, MC, SS, IC, DMCP, VMCP	[300]
	Mynocycline	-	45 mg/kg	Acute treatment	↑ in striatum	DMCP, DLCP, VMCP, VLCP, SAb	[300]
	Haloperidol + Mynocycline	-	0.8 mg/kg + 45 mg/kg	Acute treatment	↑ in striatum	ACC, MAC, MC, SS, IC, DMCP, DLCP, VLCP	[300]

Table 1. *Cont.*

Gene	Drug	D2/5HT$_{2A}$ Affinity Ratio	Dose	Duration	Effects on Gene Expression/Rat Brain Region	Brain Region of Interest	Reference
c-Fos	Haloperidol	0.00087	0.25 mg/kg 0.5 mg/kg 0.8 mg/kg	Acute treatment	↑ in striatum	VMCP, DLCP, SAb VMCP, DLCP, VLCP, SAb DMCP, DLCP, VMCP, VLCP, CAb, SAb	[288] [283,288,297]
	Haloperidol + D-cycloserine	-	0.8 mg/kg + 20 mg/kg	Acute treatment	↑ in striatum	DLCP, CAb, SAb	[297]
	Clozapine+ D-cycloserine	-	15 mg/kg + 20 mg/kg	Acute treatment	↑ in striatum	DLCP, CAb, SAb	[297]
	Clozapine	2.63	15 mg/kg	Acute treatment	↑ Nucleus accumbens	CAb, SAb	[297]
	Asenapine	3.39	0.3 mg/kg	Acute treatment	↑ in striatum	DMCP, DLCP, VMCP, VLCP, CAb, SAb	[288]
	Olanzapine	1.00	2.5 mg/kg	Acute treatment	↑ in striatum	VMCP, VLCP	[288]
	MK-801	-	0.8 mg/kg	Acute treatment	↑ in cortex	ACC, SS, IC	[314]
	Ketamine	-	25 mg/kg	Acute treatment	↑ in cortex	IC	[314]
	Ketamine	-	50 mg/kg	Acute treatment	↑ in cortex	MAC, IC	[314]
	Memantine	-	5 mg/kg	Acute treatment	↑ in cortex	MAC, SS	[314]
	Amisulpride	0.00078	10 mg/kg	Acute treatment	↑ in striatum	DMCP, VMCP	[298]
			35 mg/kg	Acute treatment	↑ in striatum	DMCP, VMCP	[298]
Zif-268	Haloperidol	0.00087	0.25 mg/kg	Acute treatment	↑ in striatum	DMCP, DLCP, VMCP, VLCP, SAb	[288]
			0.5 mg/kg		↑ in striatum	DMCP, DLCP, VMCP, VLCP, CAb, SAb	[288]
			0.8 mg/kg		↑ in striatum and cortex	DMCP, DLCP, VMCP, VLCP, CAb, SAb, M1, SS, IC	[288,298]
	Asenapine	3.39	0.05 mg/kg 0.1 mg/kg 0.3 mg/kg	Acute treatment	↑ in striatum	DMCP, DLCP, VMCP, VLCP, SAb	[288]
	Olanzapine	1.00	2.5 mg/kg	Acute treatment	↑ in striatum	DLCP, VLCP, SAb	[288]
	Amisulpride	0.00078	10 mg/kg	Acute treatment	↑ in striatum	DMCP, VMCP	[272]
			35 mg/kg	Acute treatment	↑ in striatum and cortex	DMCP, VMCP, ACC, M1	[298]
Ania-3	Haloperidol	0.00087	0.8 mg/kg	Acute treatment	↑ in striatum and cortex	DMCP, DLCP, VMCP, VLCP, SAb, ACC, MAC	[288]
					↑ in striatum	DMCP, DLCP, VMCP, VLCP, SAb, CAb	[257,260,261,267]
				Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum	DMCP, DLCP, VMCP, VLCP, CAb	[283,287]
	GBR 12909	-	15 mg/kg	Acute treatment	↑ in cortex and striatum	M2, M1, DMCP, VMCP, VLCP, SAb, PC outer, PC inner, DLCP	[283,287]
				Chronic treatment (sacrifice after 90′ from last injection)	↑ cortex	SS	
	Quetiapine	0.35	30 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum	SAb	[283]
	Aripiprazole	0.0093	12 mg/kg	Acute treatment	↑ in striatum	DMCP, DLCP, VMCP, VLCP	[287]
				Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum	DLCP, VLCP	
	Haloperidol + Escitalopram	-	0.8 mg/kg + 12 mg/kg	Acute treatment	↑ in striatum and cortex	Inner frontal cortex, DLCP, VLCP	[293]
	Haloperidol + Citalopram	-	0.8 mg/kg + 14 mg/kg	Acute treatment	↑ in striatum	DLCP, VLCP,	[293]
	Amisulpride	0.00078	10 mg/kg	Acute treatment	↓ in cortex	M1	[298]
			35 mg/kg	Acute treatment	↑ in striatum	DMCP, VMCP	[298]
mGluR5	Haloperidol	0.00087	0.8 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum and cortex	DMCP, DLCP, VMCP, ACC, MC	[286]
	Sertindole	5.37	2 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↑ in striatum and cortex	DMCP, DLCP, VMCP, ACC, MC	[286]
	SCH-23390	-	0.5 mg/kg	Acute treatment	↑ in striatum and hippocampus	DMCP, CAb, CA3, DG	[296]
αCaMKII	Haloperidol	0.00087	0.8 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↓ in cortex	MC	[286]
	Ketamine	-	12 mg/kg	Acute treatment	↑ in striatum and brainstem	DMCP, DLCP, VMCP, VLCP, CAb, SAb, SNc and VTA	[315]
Homer 2	Haloperidol	0.00087	0.8 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↑ in lateral Septum	Intermediate and ventral septum	[287]
	Clozapine	2.63	15 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↑ in lateral Septum	Intermediate septum	[287]
DAT	Ketamine Ketamine	-	12 mg/kg 50 mg/kg	Acute treatment	↑ in brainstem	SNc and VTA	[315]
Shank1	Haloperidol	0.00087	0.25 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↓ in cortex	ACC, IC	[300]
			0.5 mg/kg		↓ in cortex	ACC, IC	
	Asenapine	3.39	0.05 mg/kg		↓ in cortex and striatum	ACC, IC, VMCP, VLCP, DMCP, DLCP, CAb, SAb	[300]
			0.1 mg/kg	Chronic treatment (sacrifice after 90′ from last injection)	↓ in cortex	ACC, IC	[300]
			0.3 mg/kg		↓ in cortex	IC	[300]
ERK	Valproate	-	500 mg/kg	Acute treatment	↑ in striatum and cortex	ACC, M2, M1, SS, VMCP, VLCP, DMCP, DLCP, SAb	[289]
	Haloperidol + Valproate	-	0.8 mg/kg + 500 mg/kg	Acute treatment	↑ in striatum and cortex	ACC, M2, M1, SS, IC, VMCP, VLCP, DMCP, DLCP	[289]
	Quetiapine + Valproate	-	30 mg/kg + 500 mg/kg	Acute treatment	↑ in striatum and cortex	ACC, M2, M1, SS, DMCP, DLCP, VMCP, SAb	[289]
Norbin	Haloperidol	0.00087	0.8 mg/kg	Acute treatment	↑ in striatum and cortex	VLCP, DLCP, IC	[298]

3.4.2. PSD-95

PSD-95 is a membrane-associated guanylate kinase (MAGUK) scaffolding protein interacting with NMDAR through its NR2 subunit, AMPAR through stargazing, shaker-type potassium channels, cell adhesion molecules neuroligins (NLGNs), transmembrane protein Disintegrin, and metalloprotease 22 (ADAM22) [316–318]. PSD95 interacts also with Homer b/c long isoforms to build clusters that connect mGluRs with NMDAR [319]. PSD-95 appears to be central in the organization of the trans-synaptic complex formed by NLGN1 and neurexins, postsynaptically and presynaptically, respectively. On the other hand, it is involved in the shaping of leucine-rich glioma-inactivated protein 1 (LGI1) and ADAM22 [316,320,321] complex, controlling the fluctuation and amplitude of postsynaptic currents and, more extensively, being involved in the plasticity and strength of excitatory signaling [322–324]. Based on these observations, it is not surprising that genetic variants in the gene encoding for this protein can result in brain disorders such as intellectual disability (ID), epilepsy, hypotonia, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), movement disorders, and schizophrenia [325–335].

PSD-95 seems to have the same distribution of other constitutive genes, such as Homer1b/c, when modulated by asenapine or olanzapine, which share a receptor profile that also involves other monoamines stimulating serotonergic and adrenergic receptors. An increase was found in the signal intensity of PSD-95 throughout all subregions of the cortex and striatum, as well as in the NAc, by asenapine at different doses (0.05 mg/kg, 0.1 mg/kg, 0.3 mg/kg) as well as by olanzapine at 2.5 mg/kg [288] probably due to the progressive stimulation of dopamine, noradrenaline, and serotonin efflux in PFC and NAc related to both $5HT_{2A}$ and α_2 adrenoreceptors blockade [303]. Conversely, PSD-95 was induced in ACC and primary motor cortex (M1) by haloperidol at 0.5 mg/kg, and in ACC, supplementary motor cortex (M2), M1, insular cortex (IC), dorsomedial caudate-putamen (DMCP), dorsolateral caudate-putament (DLCP), ventromedial caudate-putamen (VMCP), core (AcCo), and shell (AcSh) of NAc by haloperidol at 0.8 mg/kg [288]. A preclinical study suggests that PSD-95 expression is significantly increased in the striatum of rats sacrificed after 90′ from the last injection in chronic administration of haloperidol and ziprasidone [284]. In rats sacrificed after 24 h, the chronic administration of ziprasidone is able to increase PSD-95 levels in the striatum [284]. Finally, both antipsychotics induce the expression of PSD-95 in the cortex at 90′ and 24 h from the last injection [284]. Chronic antipsychotic administration may significantly modulate PSD-95 expression differently from acute antipsychotics [294] according to the view that prolonged antipsychotic treatments may trigger neuroplastic changes [336], favoring the recruitment at the PSD of the molecules involved in synaptic signaling and organization. Considering the physical and functional interaction between PSD-95 and NR2A, relevant for NMDAR stabilization, NR2A-containing NMDAR leads to an attenuation of glutamate receptor signaling and a loss of the spine [255]. Given the role of PSD-95 in inhibiting D1R-mediated signaling [337], the increase in its levels may represent an indirect mechanism that contributes to reverting hyperdopaminergic conditions in schizophrenia [284]. In rats PFC, D1R, and NMDAR co-localize in single pyramidal neurons and interneurons [338]. NMDAR is not affected by the cAMP-dependent activity of D1R in primary rat prefrontal cultures. In contrast, D1R activation enhanced NMDAR-mediated Ca^{2+} release, an effect blocked by a PKA inhibitor. This finding may suggest that D1R promotes NMDAR-Ca^{2+} signaling via a PKA-dependent mechanism [338]. On the other hand, D2R stimulation is responsible for inhibiting glutamate release, reducing the excitability of medium-spiny neurons [339–341]. These opposite effects of D1R/NMDAR and D2R/NMDAR interplay in the striatum may be relevant to both the pathophysiology and treatment of schizophrenia [342]. The stimulation of D2R, as reported in schizophrenia, could worsen an already deficient NMDAR transmission in the cortical regions [342]. On the other hand, D2R blockade induced by antipsychotic drugs could restore striatal glutamatergic transmission, cortico-striatal connectivity, and synaptic plasticity, which are relevant to cognitive processes [342].

3.4.3. Shank Proteins

Shank is a PSD protein whose mutations were found to be strongly associated with ASD, ID, and schizophrenia [343], and that has been demonstrated to be instrumental in the functional and physical coupling of NMDAR and mGluR5 [344]. *De novo* mutation (R1117X) in the Shank isoform ProSAP2/Shank3 identified in a patient affected by schizophrenia is responsible for an accumulation of mutated ProSAP2/Shank3 in hippocampal neurons within the nucleus, resulting in an alteration in the transcription of several genes, such as *synaptotagmin 1* and *leucine-rich repeat transmembrane neuronal protein 1* (*LRRTM1*) and a reduction in synaptic density [345]. A preclinical study in mice also demonstrated the modulation of this molecule by antipsychotics, in particular inducing a reduction in different cortical and subcortical regions after the chronic administration of haloperidol and asenapine at different doses, confirming the view that the modulation of synaptic plasticity processes by these molecules could be finely tuned by antipsychotics depending on their doses and timing of administration [295].

3.4.4. Dopamine Regulation of Key Early Genes

There is robust evidence, embedded in almost 30 pieces of research, on the role of dopaminergic receptors in mediating the induction/activation of several IEG programs of immediate and long-lasting type [346–350]. Therefore, the possibility of exploiting early gene induction to unveil new and non-conventional targets of antipsychotic therapy is not surprising.

Activity-Regulated Cytoskeleton-Associated Protein

The activity-regulated cytoskeleton-associated protein (Arc) is an IEG encoding for a protein characterized by a C-terminus involved in the regulation of cytoskeleton structure through the interaction with F-actin [351], microtubules, and microtubule-associated protein 2 (MAP2) [352]. *Arc*-KO mice exhibit a decrease in the proportion of thin and filopodia-like protrusions as well as in the density of spines in hippocampal neurons [353], probably due to NMDAR hypofunction [354], suggesting a crucial role of Arc in the regulation of dendritic spine density and morphology [355]. Arc is also strongly modulated in multiple brain regions by antipsychotics treatment and by the different durations of drug administration: Arc mRNA expression was found to be strongly reduced in the cortex after chronic administration at the highest dose of asenapine (0.3 mg/kg) and olanzapine (2.5 mg/kg) [300], probably due to their antagonism at 5-HT_{2A} [355–358]. By contrast, haloperidol can strongly induce the *Arc* gene compared to both asenapine and olanzapine, leading to the hypothesis that an upregulation of the IEG in the striatum could be related to a perturbation of dopamine neurotransmission through D2R occupancy [286,300].

The Immediate Early Genes *c-Fos* and *Zif-268*

C-fos is a transcription factor that, when induced, forms the heterodimer activator protein-1 (AP-1), which binds to the promoter region of numerous target genes [359]. Generally, the intracellular levels of c-Fos are relatively low without any stimuli but are transiently and rapidly induced by various extracellular stimuli [360]. In this regard, it is considered a putative molecular marker of activation by antipsychotics in the brain [297]. In a previous preclinical study, the c-Fos signal was incrementally recruited in the various areas of the striatum with the increase in haloperidol doses [288], different from Zif-268, which could also explain the progressive reduction in motion related to striatum recruitment more than D2R antagonism; meanwhile, the absence of induction in cortical regions could be explained considering the scarce affinity to serotonergic receptors by this typical antipsychotic [287,288]. On the other hand, amisulpride acts as an antagonist at the D2R/D3R despite the low liability for motor side effects, which is probably due to its effects at the presynaptic terminal at a low dose (0.05 mg/kg), elicited a significant increase in c-Fos and Ania levels in the medial regions of striatum compared to vehicle, consistent with the hypothesis that this type of compound may selectively target limbic forebrain regions [298].

3.5. Intracellular Mechanisms and Antipsychotics Signaling: Non-Canonical D2R Druggable Targets in Schizophrenia

3.5.1. Modulation of Neuroprotective Molecules as Targets in Schizophrenia

Some genes involved in neuroprotection appear to be relevant for the pathophysiology of schizophrenia and other neurodevelopmental disorders and may represent novel non-canonical strategies for the treatment of these diseases. Among them, Notch Receptor 4 (NOTCH4) regulates neuronal and glial signaling and maturation [361–363], while DISC1 controls the proliferation of neural progenitors [364], modulates the positioning of pyramidal neurons in the cortex [365], and regulates the sensitization of D2R [366]. A post-mortem study on the striatum of patients affected by schizophrenia demonstrated an increased interaction between D2R and DISC1 with the formation and accumulation of intraneural complexes [367]. They are involved in a potential neuroprotective effect, and also seem to exert a modulatory effect on synaptic plasticity, which is able to decrease long-term potentiation (LTP) in the hippocampus of mice [368]. Zheng and co-authors, using FRET and stochastic optical reconstruction microscopy (STORM) techniques in murine striatal neurons, demonstrated that the D2R-DISC1 complex is also able to influence intracellular signaling and affect the growth of dendritic spines. This peculiar interaction could represent a potential D2R-mediated unconventional MOA at the dopamine receptor. In contrast, uncoupling D2R-DISC1 interaction, through the trans-activator of transcription (TAT)-D2pep (TAT-D2pep), reduced the previously discussed effect, resulting in a neuroprotective and preventive effect for neurite outgrowth and dendritic spines by associating with the downregulation of synaptophysin and PSD-95 expression [369].

Brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B (TrkB) modulate synaptic plasticity [349,370,371] and play a role in LTP [372–374]. Multiple evidence has shown that neuromuscular synapses' acute exposure to BDNF increases the frequency of spontaneous miniature excitatory postsynaptic current [375], relevant for hippocampal development [376]. BDNF also acts on hippocampal synaptic transmission, causing potentiation, probably through TrkB [377], of acute glutamate release in the presynaptic terminal [378,379] and is involved in the mobilization and docking of synaptic vesicles [380] through indirect interaction with Myosin VI (Myo6) [381,382], and TrkB via PDZ Domain Containing Family Member 1 (GIPC1), with subsequent neurotransmitter release [383]. The GIPC1 and Myo6 complex is involved in enhancing LTP at hippocampal CA3-CA1 synapses in the postnatal period and improving the synaptic plasticity processes [383], whereas Trk receptors within neurophysins are also directly involved in the modulation of dopaminergic, glutamatergic, GABAergic, and acetylcholinergic neurotransmission, representing another unconventional MOA based on the canonical neurotransmitters systems [370,378,384]. BDNF-induced glutamate release in the presynaptic terminal was also mediated by the phosphorylation of signal-regulated kinase 1/2 (ERK1/2) [379] via tyrosine phosphatase Shp-2 with subsequent neuroprotective effect [385]. In striatal neurons cultures, D1R interacts with Shp-2 determining ERK1/2 activation [386], underlining the crucial role of dopamine neurotransmission also in neuroprotective and anti-inflammatory action, and opening the possibility of identifying new uncanonical druggable molecules.

Antipsychotic Modulation of Neuroprotective Processes

Haloperidol and aripiprazole can decrease the formation of D2R-DISC1 complexes by blocking D2R, although haloperidol does not seem to significantly affect neuroprotection [387]. Ray and coauthors showed that BDNF expression was downregulated in layers IV and V of the DLPFC, layer VI of the ACC, layer VI of the inferior temporal gyrus, and layer V and/or VI of the superior temporal gyrus in patients with schizophrenia [388], and other studies have found decreased BDNF expression in the PFC and hippocampus of patients with schizophrenia [389] consistent with the hypothesis of its neuroprotective effect.

Beaulieu and colleagues showed that the increased dopaminergic stimulation of D2R results in decreased Akt activity and serine phosphorylation of glycogen synthase kinase 3 (GSK3) [390]. In coherence with their receptor profiles and D2R occupancy, aripiprazole,

clozapine, and haloperidol differentially modulate the AKT-GSK-3β cascade and subsequent dendritic plug. Clozapine and aripiprazole can increase the phosphorylation of Akt (Thr308 and Ser473) and GSK-3β (Ser9), high doses of clozapine decrease the phosphorylation of Akt, whereas haloperidol reduces the phosphorylation of both Akt and GSK-3β [273] (Table 2). Chronic high doses of haloperidol or risperidone are responsible for the down-regulation of BDNF transcripts in the hippocampus [391], and a decrease in serum BDNF concentration is reported in patients affected by schizophrenia treated with clozapine [392]. Clozapine may act through non-canonical intracellular mechanisms, for example, increasing neurogenesis in the hippocampus [393], regulating protein degeneration [394–396], and preventing apoptosis and cortical atrophy (with prevention of neural DNA fragmentation and pro-telomeric degeneration) [397–400]. Clozapine may also regulate the release of nerve growth factor (NGF) and BDNF supporting neural survival and differentiation [401–405]. Preclinical studies in rats have shown that chronic clozapine administration may enhance BDNF/TrkB signaling and increase CREB expression in the frontal cortex and hippocampus [406,407], which induces NGF participation in the processes of neuronal differentiation and growth [408] (Table 2). Signaling on CREB induced by clozapine involves two major upstream kinases, Akt and GSK-3β, going on to regulate dendritic remodeling and spine shape [409,410]. Schizophrenia patients, compared to controls, have lower levels of Akt and decreased phosphorylation of GSK-3β in the brain and peripheral lymphocytes [411]. Clozapine activates Akt [412–415] and increases the phosphorylation of GSK-3β in the PFC, striatum, and ventral midbrain [273,416,417] and appears to have an antiproliferative function through the inhibition of ErbB kinases [418] (Table 2).

Regarding antiproliferative effect, lumateperone could improve NMDAR- and AMPAR-mediated D1R signaling and increase dopamine and glutamate release in the medial PFC in rats via mTORC [419–421], regulating dopamine neurotransmission but is also involved in maintaining the integrity of the BBB and modulating molecules such as claudin-5 and intercellular adhesion molecule 1 (ICAM1) in an antiproliferative manner [421] (Table 2) (Figure 3).

Table 2. Intracellular mechanism of antipsychotic drugs and dopaminergic correlation. Abbreviations: Akt = protein-kinase B; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF = brain-derived neurotrophic factor; CREB = cAMP response element-binding protein; D2R = dopamine D2 receptor; DISC1 = disrupted in schizophrenia 1; ErbB = erythroblastic leukemia viral oncogene homologue; ERK = extracellular signal-regulated kinase; GSK3 = glycogen synthase kinase 3; mTOR = mammalian target of rapamycin; NMDA = N-methyl-D-aspartate; DAT = Dopamine transporter.

Antipsychotic Treatment	Molecular Targets	Dopaminergic Modulation	Molecular Mechanism	Biological Role	References
Aripiprazole	Akt Thr308 and Ser473 and GSK-3β Ser9 phosphorylation	D2R-signaling	AKT-GSK-3β cascade	Neuroprotective action	[273,390]
Aripiprazole, haloperidol	decrease D2R-DISC1 complexes	D2R-signaling	DISC1	Neuroprotective action	[387]
Clozapine	BDNF-CREB	D2R-signaling	decreased Akt activity and phosphorylation of GSK3	Neuronal survival and regulation of synaptic plasticity	[390,412,413]
	NMDAR	DAT	Akt-GSK3	Neuroprotective action	[422,423]
	Akt Thr308 and Ser473 and GSK-3β Ser9 phosphorylation	D2R-signaling	Akt-GSK-3β cascade	Neuroprotective action	[273,390]
Clozapine, olanzapine, quetiapine	ErbB kinases, PIK3CD	D2R-signaling	ErbB4-PI3K-Akt pathway	Antiproliferative, neuroprotective action	[424] [425]
Haloperidol	Akt Thr308 and Ser473 and GSK-3β Ser9 phosphorylation.	D2R-signaling	Akt-GSK-3β cascade	Neuroprotective action	[273,390]
	ERK1/2	D2R-signaling	Akt/mTOR pathway	Neuroprotective action	[426]
Lumateperone	NMDA and AMPA receptors	D1R-signaling	mTOR pathway	Neuroprotective role	[426]

3.5.2. Neuroinflammation Mechanisms in Schizophrenia

During inflammatory processes, quinolinic acid and kynurenic acid are mainly synthesized in microglia and in astrocytes, respectively. The first is an NMDAR agonist with potential excitotoxicity [427], while the second is an NMDAR antagonist [428] that could induce cognitive dysfunctions, consistent with the NMDAR hypofunction hypothesis of schizophrenia [429–431]. These molecules, together with the excess in glutamate levels, can induce excitotoxic effects on oligodendrocytes and, consequently, alterations in myelination processes, inducing alterations in the transmission of GABAergic interneurons that terminate on dopaminergic projections in the striatum [432,433].

Preclinical studies in mice showed that maternal immune activation affects dopamine receptor expression, increasing dopamine levels in the striatum and decreasing D2R levels in adult offspring [434,435]. Alterations in cytokine homeostasis may correlate with the pathogenesis of schizophrenia, probably with a link to alterations in dopaminergic and glutamatergic signaling [435]. IL-1β appears to result in abnormal glutamate release and subsequent neurotransmitter accumulation that induces neuronal death [436]. Studies on rats showed that IL-1β results in the transformation of mesencephalic progenitor cells into a dopaminergic phenotype [437,438], while IL-6 can reduce the survival of serotonergic and dopaminergic neurons [439,440]. Tumor necrosis factor (TNF)-α can cause dopaminergic neurodegeneration with neuronal damage in the striatum [441]. Several cytokines play a role in neurotoxicity and appear to correlate with TRS and potentially to dopaminergic transmission with a pro-inflammatory role: IL-12A that induces an increase in the cytotoxic activity of NK cells and T cells [442,443], IL-18 [444,445], and IL-8 that increases the migration of neutrophils, T lymphocytes, and monocytes [446–448], and IL-17 that promotes macrophage and microglia activation [442,449,450]. On the other hand, multiple cytokines exhibit an immunosuppression function: IL-4 increases Th2-mediated cytotoxicity and promotes switching from T-helper to Th2, also modulates macrophage and microglial cell action [451,452], IL-6 modulates the sensitivity of neurons to neurotransmitters [453–455], and IL-10 activates JAK1 and STAT3 and induces expression of immunosuppressor genes [442,456–459]. In addition, TRS patients could have non-dopaminergic mechanisms underlying the disorder, and non-canonical druggable mechanisms could even include neuroinflammatory processes [460].

Dopamine may modulate the activity, migration, differentiation, and proliferation of immune cells [461–464]. Tetrahydrobiopterin (BH4), a cofactor for tyrosine and dopamine synthesis, can regulate inflammatory cytokines, which in turn modulate the expression of GTPcyclohydrolase 1 (GCH-1), a cofactor for BH4 production [465]. During inflammation, there is a reduction in BH4 synthesis, resulting in decreased dopamine levels; it has been hypothesized that this process is triggered by oxidative processes, ROS, and cytokines (IFN-α, IL-6, and cardiotrophin-1). In contrast, IL-1β, IFN-γ, and TNF-α can increase dopamine levels by increasing BH4 [466,467].

3.5.3. Antipsychotics and Their Potential Anti-Inflammatory Effects

Multiple first- and second-generation antipsychotics may decrease oxidative stress by blocking the release of proinflammatory cytokines from activated microglia [468].

Maes and colleagues demonstrated that patients with TRS had dysregulation cell-mediated immunity with increased monocytic activity [469]. Fernandez-Egea et al. showed that patients affected by schizophrenia have increased numbers of natural killer cells, naïve B cells, memory T cells, and monocytes and decreased numbers of dendritic cells, regulatory T cells, and $CD4^+$ T cells in the blood [470]. Typical antipsychotics decrease the plasma levels of IL-6 and IL-6 receptor (IL-6R) [471], while atypical antipsychotics, such as clozapine and risperidone, increase the concentrations of IL-2R, IL-6, and TNF-α [435,472,473]. Clozapine has been demonstrated to interfere with multiple steps of the inflammatory response [474] and inhibit microglial activation [475]. Here, the most relevant anti-inflammatory effects of clozapine are reported: (1) increases IL-6, CC16, and IL-1 receptor antagonist (IL-1Ra) in subjects affected by schizophrenia [472]; (2) inhibits lymphocyte proliferation and production of IL-2, interferon-(IFN)γ, and IL-4 [476]; (3) attenuates the neuroinflam-

matory response, $CD4^+$ T cells of patients treated with clozapine, exhibit an increase in *DRD3* expression [470]; (4) activates the docosahexaenoic acid anti-inflammatory cascade [477]; (5) inhibits Ca^{2+}/CaM/Akt-mediated nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) [478] and prevents mast cell degranulation in the CNS [479]; (6) regulates cytokine homeostasis [480–484]; and (7) inhibits Akt phosphorylation induced by cytokines released in inflammatory processes [485]. Akt, in turn, can inhibit GSK3 by modulating the level of NMDAR and reducing dopamine concentration in the synapse by increasing DAT activity [422,423]. Finally, lumateperone can modulate serotonergic, dopaminergic, and glutamate neurotransmission (Figure 3), also affecting neuroinflammatory biomarkers by reducing the levels of proinflammatory cytokines such as IL-1b, IL-6, and TNF-α in both the brain and serum [421].

3.6. Intracellular Signaling in Schizophrenia: Implication for Dopamine Transmission

A post-mortem study showed that in the PFC of schizophrenia patients, there was an increase in NRG1-induced ErbB4 activation and increased ErbB4/PSD-95 interaction, responsible for the suppression of NMDAR signaling activation [486]. The NRG-ErbB4 signaling pathway regulates dopaminergic and GABAergic transmission and blocking ErbB signaling increases dopamine levels in the striatum [487].

D2R in the striatum may activate the phospholipase C (PLC)/inositol trisphosphate (IP3)/calcineurin signaling pathway and modulate the excitability of GABAergic neurons through the regulation of presynaptic L-type Ca^{2+} channels [488]. Alterations in the regulatory subunits (CNB1 and CNA) of calcineurin can induce changes in vesicle release kinetics through modulation of Ca^{2+} influx from N-type Ca^{2+} channels [489]. Calcineurin is also able to disinhibit protein phosphatase 1 (PP1) [490], which in turn is regulated by dopamine- and cyclic adenosine monophosphate (cAMP)-regulated phosphoprotein, 32 kDa (DARPP-32) strongly expressed in striatal projection neurons [491,492]. DARPP-32 is a cytosolic protein highly expressed in medium spiny neurons of the neostriatum, functioning as an integrator between cortical input and the basal ganglia [493]. Specifically, it has been implicated in schizophrenia proposing its phosphorylation, mediated by dopamine and glutamate signaling, as a potential non-canonical therapeutic target [493]. In addition, preclinical studies on the PFC of schizophrenia animal models have reported decreased levels of DARPP-32 [494], whereas post-mortem clinical studies on the superior temporal gyrus and DLPFC of schizophrenia patients have found a reduced expression [495,496]. In addition, it has demonstrated increased phosphorylation of DARPP-32 during therapy with antipsychotic drugs, such as haloperidol [497–499], resulting in improved behavioral performance in animal models. On the other hand, preclinical evidence has shown that D2R can directly activate calcineurin [500], which binds to D1R [501]. These findings suggest the possibility that calcineurin could be a non-canonical target for antipsychotic drugs in patients with schizophrenia [502].

Antipsychotic Modulation of Dopamine Intracellular Signaling

Multiple lines of evidence have found a link between antipsychotic drugs and epidermal growth factor (EGF) through the signaling of the mitogen-activated protein kinase extracellular signal-regulated kinase (MAPK)-ERK cascade [497,503]. Clozapine induces ERK activation via EGF receptor phosphorylation [504], and it is implicated in ERK1/2 activation, playing a crucial role in synaptogenesis processes and synaptic plasticity [416–418,505]. The acute administration of clozapine or haloperidol decreases the activation of proline-rich, extensin-like receptor kinase (pERK)-1 in primary PFC neuronal cultures, whereas clozapine only stimulates pERK1 and pERK2 not affecting the canonical dopamine D2R-$G_{i/o}$-PKA or serotonin $5HT_{2A}$-G_q-PLC signaling pathways [504]. Dopamine receptors are G-protein-coupled receptors belonging to two main subfamilies: D1R-like (e.g., D1R and D5R) and D2R-like (e.g., D2R, D3R, and D4R). D1Rs activate cAMP via their coupling to G_s/G_{olf}, whereas D2Rs are bound to $G_{i/o}$ and release $G\alpha_{i/o}$ and $G_{\beta\gamma}$ subunits. Canonically, the function of D2R is implicated in antagonizing cAMP-dependent signaling by inhibiting the activation of PKA [506,507]. In

striatal neurons, DARPP-32 is a primary target of PKA and is involved in dopaminergic activity, including the inhibition by D2R of the cAMP-dependent pathway [508]. In this context, β-arrestin is involved in the internalization of the receptor through a complex consisting of Akt, β-arrestin 2, and PP2A phosphatase, demonstrating a key role in the regulation of Akt and GSK [37,390]. Beaulieu and colleagues suggested that the D2R/Akt/β-arrestin pathway might contribute to the dopaminergic dysregulation consistent with the pathophysiology of schizophrenia [390,509]. From a behavioral perspective, genetic KO mice for β-arrestin 2 and GSK reduced acute locomotor response to psychostimulants and exploratory activity [510]. Together, these findings opened new directions for investigating D2R-mediated and cAMP-independent non-canonical intracellular pathways, where alterations in Akt and GSK could be relevant to schizophrenia [509]. On the other hand, dopamine firing was also modulated by serotonin neurotransmission that represents, via $5HT_{2A}$-G_q-PLC, the other canonical target of choice for antipsychotics, for second-generation antipsychotics [511]. Through $5HT_{2A}$ blocking dopamine efflux in all regions of the brain with an excitatory function was facilitated, potentiating dopamine neurotransmission in cortical regions and leading to reduction of dopamine release in the mesolimbic areas that contributes to antipsychotics canonical activity [511].

A preclinical study in the rat cortex and striatum showed that the acute administration of clozapine increased c-Fos levels and induced biphasic phosphorylation of 90 kDa ribosomal s6 kinases (p90RSKs) by MEK/ERK independently of EGF receptor blockade [512]. In contrast, haloperidol and olanzapine resulted in the phosphorylation of p90RSK without ERK signaling [512]. Haloperidol was able to regulate c-Fos expression in the striatum in accordance with the transcriptional regulation of ERK [512]. Clozapine's properties in modulating the expression of nuclear targets of the ERK cascade, differently from haloperidol and olanzapine, demonstrate a novel signaling pathway that may be relevant as an unconventional mechanism in the treatment of TRS when failure of canonical antipsychotics occurs.

The upregulation of transcripts of the NRG-ErbB signaling pathway in schizophrenia is reported [513], and it has been hypothesized that the abnormal expression of NRG and ErbB4, through the modulation of GABAergic and dopaminergic neurons, may contribute to the onset of schizophrenia is probably via an ErbB4-mediated mechanism exploiting PI3K/Akt signaling [514]. Karbownik and colleagues showed that in glioblastoma cells, and at a dose comparable to ones considered efficacious, clozapine, olanzapine, and quetiapine decreases the mRNA expression of *phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta* (*PIK3CD*), a gene encoding for the delta catalytic subunit of PI3K by going on to alter the ErbB4-PI3K pathway [424]. This intracellular signaling has been identified as a possible unconventional molecular target for the treatment of schizophrenia [424]. Liu and coauthors highlighted the correlation between the DRD2-PI3K-AKT signaling cascade and the pathogenesis of schizophrenia [425].

Finally, antipsychotics drugs may regulate the AKT/mTOR pathway by directly affecting dopaminergic signaling: changes in striatal dopamine neurotransmission are caused, at least in part, by elevated D2R expression and upregulated ERK1/2 activation suggesting the implication of mTOR complex 2 (mTORC2) signaling as a non-canonical pathway in regulating striatal dopamine tone and D2R signaling [426].

3.7. An Emerging Field: The Repositioning of Antipsychotics in Medicine Implication for Non-Canonical Mechanisms

An ongoing search exploits the possibility of repurposing antipsychotics for the treatment of medical conditions other than psychiatric diseases, such as cancer [515–517]. These studies could shed light on new non-canonical MOA of antipsychotics that may be crucial also in the development of novel druggable targets in schizophrenia.

According to this possibility, here we consider non-canonical MOAs of first- and second-generation antipsychotics under evaluation for cancer and other diseases.

Chlorpromazine antagonism at the D2R [518] could play a further role in controlling the growth of certain neoplastic diseases. Chlorpromazine has been identified as a potential candidate for drug repurposing in glioblastoma by inhibiting cell growth and proliferation

and controlling mitochondrial mechanisms related to the growth of this type of cancer [515]. This drug induces, in glioma cells, both autophagic cell death via the inhibition of the PI3K/AKT/mTOR pathway [519] and cycle arrest in the G2/M-phase by increasing the expression of the cyclin-dependent kinase (CDK) inhibitor P21 [520]. Colorectal cancer is another type of tumor in which chlorpromazine may have a role in being capable of causing both the upregulation of P53 with subsequent apoptosis and the inhibition of mitotic kinesin KSP/Eg-5 with mitotic arrest [521]. In ovarian cancer, it may induce cell apoptosis by the AKT-dependent activation of GSK3β or B cell lymphoma 2 agonists of cell death (Bad) [522]. Recently, based on the results of preclinical studies, a phase II clinical trial was conducted combining chlorpromazine 50 mg/day to the standard treatment with temozolomide in the sole adjuvant phase of the standard protocol in 41 diagnosed glioblastoma multiforme patients carrying a hypo-methylated *O6-methylguanine-DNA-methyltransferase* (*MGMT*) gene [523]. It was demonstrated that chlorpromazine, along with levomepromazine and thioridazine, promotes cancer stem cell differentiation via the dopamine receptor pathway; these drugs are also involved in the inhibition of mitochondrial DNA polymerase and are responsible for a decrease in ATP production with selective cytotoxicity and antiproliferative activity in leukemic cells [524–527]. Chlorpromazine appeared to inhibit both the AMPAR [528], relevant for glioblastoma multiforme growth and progression [529], and NMDAR [528] involved in the nesting and growth of brain metastases from breast cancer [530]. A preclinical study for the potential treatment of triple-negative breast cancer and its brain metastases showed that fluphenazine hydrochloride induces downregulation in the expression of cyclin-dependent kinases (CDK) 2, CDK4 and cyclin D1 and the up-regulation of P21 and P27, as well as intrinsic mitochondria-mediated apoptosis in vitro through the induction of G0/G1 cell cycle arrest [531]. Furthermore, fluphenazine hydrochloride is also able to decrease the expression of p44/42 ERK and phosphorylate AKT, involved in the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways, relevant for triple-negative breast cancer, resulting in the suppression of the growth and survival of cancer cells [531]. Considering its antiproliferative effects, in previous years were conducted two clinical trials in 30 patients affected by refractory advanced multiple myeloma to evaluate the safety and tolerability as well as the side effects and best dose of the drug [532,533]. Penfluridol has been explored for the inhibition of cancer metastasis through the action of integrin expression responsible for the suppression of the epithelial-to-mesenchymal transition factors, vimentin, and zinc finger E-box-binding homeobox 1 [534]. The decrease in the levels of integrin α6 and urokinase-type plasminogen activator receptor in glioma cells induced by penfluridol via focal adhesion kinase, paxillin, RAC, and Rho-associated coiled-coil containing kinases proteins activation was found reducing cancer cell migration and invasion [534]. These antiproliferative effects could also be mediated by suppressing cancer growth via the AKT-dependent inhibition of the transcription factor *glioma-associated oncogene 1* [534]. Trifluoperazine acts as a calmodulin antagonist; its involvement in calcium homeostasis has been reported in liver and breast cancer therapy based on the elevated levels of Ca^{2+} and calmodulin typical of these cancers' cell types, which are associated with increased DNA synthesis and cell proliferation. This drug is found to bind the IP3 (inositol 1,4,5-trisphosphate) receptor, promoting Ca^{2+} release from the endoplasmic reticulum and subsequent cell death [535] and acting as a calmodulin antagonist. It prevents calmodulin–isocitrate dehydrogenase binding that is relevant for the survival and migration of glioblastoma multiforme cells [535]. Finally, trifluoperazine enhanced the effects of doxorubicin on glioma cell growth by increasing the expression of the nuclear tumor suppressor Forkhead box O1 and reducing the levels of multidrug resistance genes [536]. Another example of drug repositioning is represented by pimozide, which through its effect as an antagonist at D2R, D3R, and D4R, has been used to explore the potential anti-metastatic activity in murine melanoma [537]. The epidermal growth factors epiregulin, epigen, and NRG1 are discovered to be downregulated as a result of pimozide's inhibition of the phosphorylation of signal transducer and activator of transcription (STAT)5 in breast cancer cells [538]. Instead, by targeting the STAT3 signaling pathway, pimozide

was found to inhibit proliferation and promote apoptosis in prostate cancer cells [539]. Finally, this drug may weaken the self-renewal and survival of glioblastoma multiforme, inhibit myelin-related infiltration, and increase sensitivity to radiotherapy by acting on the ubiquitin-specific peptidase 1-inhibitor of DNA binding proteins-Nogo ligand1 signaling axis [540,541]. Olanzapine has been reported to have an antiproliferative action and can inhibit glioblastoma cell proliferation, migration, and anchorage-independent growth. Furthermore, it might induce autophagic cell death through the suppression of NF-κB activation [542] and disrupt cholesterol homeostasis, resulting in cell death [543]. Risperidone induces a reduction in PC3 prostate cancer cell proliferation rate in adenocarcinoma [544]. Clomipramine induces the phosphorylation of c-Jun and an increase in cytochrome c release and caspase-3-like activation, leading to the apoptosis of glioblastoma cells [545]. Clozapine seems to have potential adjuvant anticancer activity for the treatment of human breast cancer and metastatic melanoma via the H4 receptor [546–548], reducing the growth/survival rates of human astroglioma cells in a dose-dependent manner, as also seen in rat cortical neurons [418] through ErbB kinase inhibition [549].

The potential efficacy of dopamine receptor antagonists, especially at D2R, in cancer therapy, is still in its infancy, and the role of dopamine in cancer biology is worth further exploration [550]. The efficacy of anticancer drugs in breast and colon cancer by dopamine signaling [551], the evidence that polymorphisms of the DR2 modulate the risk of colorectal cancer [552], as well as studies that exhibit a reduction in cancer incidence among schizophrenia patients treated with antipsychotics, add more [553–560].

4. Discussion

Although all antipsychotics share the common feature represented by D2R occupancy, which is considered the major mechanism of the "anti-psychotic" effect, in recent years, other cellular mechanisms based on dopaminergic function, its modulation, and non-canonical type have emerged [46,67,174,349,561,562]. Greater precision in defining the molecular and structural nature of dopamine receptors' interaction with the antipsychotic molecules (e.g., the atomistic molecular dynamics simulations of typical and atypical antipsychotics and the cryoelectronic microscopy structures of D1R-G_s and D2R-G_i signaling complexes) has also open new avenues to understanding the "dopaminergic side" of antipsychotic action allowing [563,564]. The discovery of different dopaminergic mechanisms at D2R has opened new scenarios of the pharmacological mechanisms, possibly for patients who do not respond or respond poorly to antipsychotics. A relevant change in the canonical conceptualization of dopamine dynamics under antipsychotic exposure is the appreciation of novel presynaptic mechanisms related to dopamine release regulation that is believed to be the major pathogenetic underpinning responsible for hyperdopaminergia in schizophrenia [565]. One of these presynaptic mechanisms is the accumulation of the antipsychotic drug in synaptic vesicles with the endogenous dopamine and its subsequent release upon neuronal activation in extracellular space where the antipsychotic inhibits VGSCs and vesicular exocytosis [78,79]. It has been reported that haloperidol may enhance the activity of VGSCs in cortical neurons in cortical slices after chronic exposure [566], whereas acute haloperidol treatment may induce channel inhibition [567]. It has been suggested that this action upon VGSCs may contribute to time-dependent both therapeutic effects and side effects of haloperidol. A significant effect on VGSCs is also reported for the bias-ligand aripiprazole [568]. Concerning the dopaminergic presynaptic mechanism, DAT has also been implicated for its potential involvement in antipsychotics' response despite the fact that its role in schizophrenia pathophysiology is still elusive partly due to methodological limitations both at clinical and preclinical levels [5,569–571]. Beyond intracellular dopamine D2-directly mediated signaling, dopamine-dependent trans-synaptic mechanisms have emerged, unveiling antipsychotics' impact on the expression and functions of molecules belonging to different neurotransmitter systems. Among the trans-synaptic effects of antipsychotics, the modulation of the gene expression of glutamatergic PSD proteins has attracted attention for the potential relevance of directly sculpting the synapse

architecture based on the pivotal role of PSD proteins in shaping the dendritic spine. It has been demonstrated that PSD proteins, such as PSD-95, Homer, and Shank, are involved in schizophrenia pathophysiology and that their gene expression is modulated by antipsychotics based on the D2R affinity, dose, and duration of treatment, whereas the specific receptor profile beyond dopamine D2R antagonism may further contribute to modulate the pattern of gene expression changes [349]. A critical appraisal of the findings reported in the present systematic review should also consider some limitations and open questions. First, when considering canonical and non-canonical mechanisms of antipsychotics focusing on dopamine, it is probably a reductionistic approach for drugs that have a complex receptor profile. Despite the significant role of other neurotransmitter systems, above all, the glutamatergic [572,573], GABAergic [574], and serotoninergic [82] ones; dopamine remains a pivotal target for schizophrenia treatment [575,576]. Furthermore, the search for dopamine-based non-canonical mechanisms is particularly timing considering the emerging novel concepts on dopamine molecular anatomy [577] and physiology relevant for the pathophysiology and clinics of salience and cognition mechanisms [578], possibly involved in the clinical manifestations of schizophrenia, especially in terms of abnormal cortical-subcortical connectivity [579]. Among these new findings, the repurposing of dopaminergic functional anatomy beyond the classical pathways has been noted [580] and the demonstration of the involvement of nigrostriatal pathways not only in positive symptoms, as already known, but also in cognitive and negative symptoms of psychosis in a more direct way than previously thought [581].

Second, it could be questioned if and how non-canonical mechanisms can be pragmatically tackled for the development of novel therapeutic strategies that are needed for those conditions, such as TRS, that do not respond or respond poorly to the available antipsychotics. In this regard and concerning presynaptic dopamine regulation, at least two compounds are in an advanced phase of clinical development represented by TAAR1 agonist [174,582–585] and xanomeline + trospium [168,169,585,586], both involved in the regulation of dopamine release, though not through a primary dopamine-dependent receptor mechanism. Furthermore, regarding the modulation of synaptic proteins that are a significant non-canonical dopamine-dependent effect of antipsychotics, it should be acknowledged that despite the technical difficulties, there is a growing interest in the possibility of interfering with the PSD proteins' function. A relevant example is represented by PSD-95 inhibition by *N*PEG4(IETDV)2 (Tat-*N*-dimer), which binds the tandem PDZ1-2 domain of PSD-95 with a high affinity of 4.6 nM [587,588] in the same line of research is the development of the small molecules ZL006 and IC87201 as potential inhibitors of nNOS-PDZ/PSD95-PDZ interactions [589].

Third, an open question of clinical relevance is to what extent novel mechanisms based on non-canonical dopamine-related MOA can be "game-changing" in those difficult-to-treat conditions such as TRS. At present, the xanomelin + trospium combination is under scrutiny in a clinical trial specifically designed for subjects with schizophrenia with an inadequate response to their current antipsychotic treatment [590], and any prediction should be held until the final results are publicly available. With caution, it is conceivable that regulating dopamine release with a non-primary dopamine mechanism could be efficacious for those cases of resistance that emerged after a period of a successful response to antipsychotics' treatment and believed to be linked, possibly, to the upregulation of D2R (increased B_{max}) and/or D2R high affinity increased number.

5. Conclusions

Antipsychotics' dopamine-based non-canonical mechanisms should be exploited (i) for a better understanding of the complex cellular dynamics of antipsychotics beyond D2R occupancy-driven signaling (i.e., cAMP, β-arrestin/AKT and Phospholipase A); (ii) to overcome the limitations, in terms of both efficacy and adverse events of the available compounds. This could allow the exploration of new molecular avenues within the

dopamine system, which remains, directly or indirectly, a fundamental pharmacological target in schizophrenia treatment.

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