Pharmacological Research 176 (2022) 106078

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Present and future antipsychotic drugs: A systematic review of the putative mechanisms of action for efficacy and a critical appraisal under a translational perspective

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ARTICLE INFO

Keywords:
Dopamine
Antipsychotic drugs
Signaling pathways
Treatment resistant schizophrenia
Synaptic mechanisms
Neuronal plasticity

ABSTRACT

Antipsychotics represent the mainstay of schizophrenia pharmacological therapy, and their role has been expanded in the last years to mood disorders treatment. Although introduced in 1952, many years of research were required before an accurate picture of how antipsychotics work began to emerge. Despite the well-recognized characterization of antipsychotics in typical and atypical based on their liability to induce motor adverse events, their main action at dopamine D2R to elicit the "anti-psychotic" effect, as well as the multimodal action at other classes of receptors, their effects on intracellular mechanisms starting with receptor occupancy is still not completely understood. Significant lines of evidence converge on the impact of these compounds on multiple molecular signaling pathways implicated in the regulation of early genes and growth factors, dendritic spine shape, brain inflammation, and immune response, tuning overall the function and architecture of the synapse. Here we present, based on PRISMA approach, a comprehensive and systematic review of the above mechanisms under a translational perspective to disentangle those intracellular actions and signaling that may underline clinically relevant effects and represent potential targets for further innovative strategies in antipsychotic therapy.

1. Introduction

The origin of antipsychotics (APs) treatment is usually dated in 1952 with the introduction in the clinics of chlorpromazine that is regarded as the prototypical "typical" APs [1], which was followed by the marketing of many other typical antipsychotics. In the Seventies, the introduction of clozapine represented a significant novelty for the behavioral effect of the drug at preclinical and clinical level. However, paradoxically, it was after the withdrawal and its subsequent re-introduction in the 1990s that this compound became fully appreciated for its claimed superior efficacy and gained a unique role as the medicine of choice in Treatment-resistant Schizophrenia [2], although the potentially life-threatening side effects and the need for intense monitoring have significantly limited its use.

Finally, it was only in 2003 that the approval of aripiprazole opened a new strategy based on its partial agonism at dopamine receptor D2 (D2R) and D3 (D3R) [3].Typical APs (i.e., haloperidol, fluphenazine, perphenazine) are mainly characterized by high affinity as antagonists at D2R and a clinically relevant liability to induce movement disorders [4]. On the other hand, atypical APs exert their effect acting on multiple receptors, and the ratio between the affinity of D2R and serotonin or 5-hydroxytryptamine (5-HT) 2A receptors (5-HT2A) has been considered crucial both for efficacy and for reducing the liability of motor side effects [5]. Even if this dual envision of APs categories has become popular, several issues call for a revision of the present classification based on their putative mechanism(s) of action. Here are some controversial points.

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https://doi.org/10.1016/j.phrs.2022.106078
Received 12 November 2021; Received in revised form 23 December 2021; Accepted 7 January 2022
Available online 10 January 2022

a) While considered as a feature of atypical APs, even some typical compounds, such as chlorpromazine share a certain degree of binding at the 5-HT2A [6].
b) Despite falling into the category of typical APs, benzamides (i.e., amisulpride) do not commonly elicit significant motor side effects [7].
c) The liability to induce motor adverse events depends on the dose rather than the class of APs [8].

Therefore, nearly 70 years after chlorpromazine was marketed, the mode of action of APs remains in some aspects an enigma difficult to decode, and despite many years of research, an accurate picture of how APs work is struggling to emerge. For instance, the action of APs may be intimately related to their 3d or chemical structure, as well as their receptor binding profile, receptor-initiated downstream intracellular mechanisms resulting in a sequence of biochemical events, modulating enzyme activity and gene expression. In view of the large number of molecular targets that may be regulated by APs [9], here we present a summary of the latest advancements in their pharmacodynamic knowledge, based on PRISMA approach, in order to disentangle among the above molecular mechanisms those that may underline clinically relevant effect and represent potential targets for further innovative strategies in AP therapy.

2. Methods and search strategy

The aim of this systematic review was to explore the clinical and preclinical evidence available on the unveiled mechanisms of action of APs. English-written articles investigating the pharmacodynamic properties and mechanisms underlying the therapeutic effects of APs, published in peer-reviewed journals in the last decade and available in the PubMed database, were included. Only papers reporting original data were deemed eligible, whereas review papers and commentary were excluded. Articles investigating mechanisms underlying the development of side effects or adverse events of APs, but not related to their therapeutic efficacy, were not considered relevant to the subject. The search strategy and data collection were managed in adherence with the PRISMA-P (Preferred Reporting Items for Systematic Review and MetaAnalysis Protocol) 2015 checklist. We performed a comprehensive search in the PubMed database on 3 August 2021, using a search string combining 49 different related words (see the Supplemental Text for more details) and filtering results by language (English) and publication date, thus selecting those published in the last 10 years. The search returned 4446 records that were managed by Endnote X and screened by title and abstract. Eligible papers were selected for full-text assessment in adherence with the inclusion criteria (see Prisma-P flow-diagram in the Supplemental text). Adjunctive records retrieved from other sources were 26. Sources included in the qualitative synthesis were 214.

3. Receptor binding profile of APs

The entire class of APs typically acts on post-synaptic D2R, making challenging the identification of molecules with antipsychotic activity devoid of a significant D2R affinity. Despite the fact that D2R blockade has historically been viewed as the main feature of APs, in the last twenty years novel APs acting as partial agonists at this site have been marketed [10]. Moreover, most APs interact with a wide range of receptor targets (Table 1).

3.1. Dopamine receptors

Almost all available APs bind to D2R [11]. Indeed, D2 antagonism has long been associated with APs ability to reduce the salience attribution to sensory irrelevant symptoms, which underlie positive symptoms [12,13]. Human Positron Tomography Emission (PET) studies suggests that APs effects occur within the therapeutic window ranging from 60% to 80% of D2-like striatal receptor occupancy [14,15] strongly correlating their clinical efficacy with a substantial degree of D2R occupancy.

Table 1
Receptor targets of APs and putative clinical effects they may mediate.

Receptor	APs action	Putative target symptoms
D1	agonism	negative symptoms
D2	antagonism/partial agonism	positive symptoms
D3	antagonism/partial agonism	cognitive and negative symptoms
D4	antagonism	cognitive and negative symptoms
5-HT1A	agonism	cognitive, anxiety and depressive symptoms
5-HT2A	antagonism	negative symptoms
5-HT7	antagonism	cognitive, anxiety and depressive symptoms
α7nACh	agonism	cognitive symptoms
AchMR1/4	agonism	positive and negative symptoms
H1	antagonism	agitation, anxiety symptoms
α1	antagonism	positive symptoms
α_{2c}	antagonism	cognitive, negative and depressive symptoms
mGluR2/3	agonism and allosteric modulation	cognitive symptoms
σ_1	antagonism	negative symptoms
TAAR1	agonism	positive, negative and cognitive symptoms

Aripiprazole, brexpiprazole, and cariprazine are representative of a new class of APs that act as “dopamine stabilizers”, namely partial agonists at D2R/D3R [16]. Partial agonists may act as functional agonists or antagonists, depending on the surrounding levels of endogenous ligand. According to this view, D2R partial agonists may act as functional antagonists within the mesolimbic system, where a hyperdopaminergic state may contribute to positive symptoms; on the other hand, they act as functional agonists in the mesocortical pathway, where extracellular dopamine levels are low, thus mitigating, or at least not worsening, negative and cognitive symptoms [17,18]. Among the novel D2R partial agonists differences also exist. Brexpiprazole has the strongest affinity for D2R, followed by aripiprazole and cariprazine [19]. However, brexpiprazole displays lower intrinsic activity at D2R compared to aripiprazole, thus may exhibit fewer activating adverse effects [20].

Unlike other APs, a newly available compound named lumateperone behaves as a partial agonist at presynaptic DR2 and as an antagonist at postsynaptic D2R [21]. The blockade of presynaptic D2 autoreceptors is responsible for a massive perturbation of the dopaminergic striatal neurotransmission, affecting dopamine turnover, tyrosine hydroxylase phosphorylation, and dopamine overflow [22,23]. In this view, lumateperone may dampen striatal dopamine neurotransmission disruption without producing motor side effects.

Clinically active doses of risperidone, haloperidol, olanzapine, and even clozapine failed to reach a relevant degree of D3R occupancy in vivo, despite the near-equivalent in vitro affinity of these agents for D2R and D3R [12,24]. However, given that D3Rs are abundantly expressed in brain regions involved in the regulation of motivation and reward-related behaviors such as the ventral striatum [25], APs with preferential binding to D3R over D2R (e.g., cariprazine, which acts as a D3R/D2R partial agonist) are thought to be effective against a greater range of symptoms of schizophrenia, especially cognitive and negative ones [26–30]. Consequently, D3R has raised interest as a potential key target for treating negative symptoms in subjects affected by schizophrenia [31].

Prefrontal dopamine transmission through D1R is believed to play a role in the pathophysiology of cognitive and negative symptoms of schizophrenia [32,33], although pharmacological manipulations of D1R have led to inconsistent results [34,35]. Certain APs also act on D1R, behaving as inverse agonists (e.g., chlorpromazine, fluphenazine,

haloperidol) or agonists (e.g., clozapine) at this site [36,37]. Downstream cellular events triggered by D1R activity appear to involve voltage-gated calcium channel (CaV2.2) and ionotropic glutamate receptors. In fact, D1R may physically interact with CaV2.2 and stabilize channels within the membrane, thus modulating the activity-mediated calcium influx and participating in synaptic plasticity events [38]. As revealed by the experience of lumateperone, a novel compound targeting D1R, a secondary effect of D1R activation is an increase in phosphorylation of the N-methyl-D-aspartate receptor (NMDAR) $GluN_{2B}$ subunit, leading to enhanced NMDAR activity and responses [39,40].

D4R is mainly located in mesolimbic and mesocortical areas, rather than in the basal ganglia, thus representing an anatomical selective dopaminergic target for APs devoid of extrapyramidal symptoms [41]. It has been suggested that clozapine's superior effectiveness may indeed originate from its peculiar affinity for D4R (Ki = 39 nM) [42]. Nonetheless, the role of D4R in psychosis remains to be clarified and conflicting evidence is found in the literature [43–45].

3.2. Serotonin receptors

5-HT2A receptors have gained considerable interest since the 1980s, when atypical APs began to emerge. In fact, the majority of atypical APs block 5-HT2 receptors which are responsible for the inhibition of dopamine release. Thus, their blockade in the frontal cortex, where their expression is abundant despite dopamine receptors, may mitigate the 'hypodopaminergia' underlying negative symptoms [46]. Similarly, 5-HT2A antagonism may attenuate the extent of the AP-induced dopamine deficiency at striatal level, which contributes to extrapyramidal side effects. Therefore, it has been proposed that ratio values of pKi for 5-HT2A/D2R close to 1 (Meltzer's ratio) are predictive of an atypical antipsychotic profile [47]. Clozapine shows a very high 5-HT2/D2 ratio (20 times higher affinity for 5-HT2 than for D2) in comparison with other APs [48], although the novel drug lumateperone displays an affinity for 5-HT2A approximately 60 times higher than for D2R [21].

Beyond the antagonism at 5-HT2A receptor, modulation of other serotonergic receptors by APs appears to be relevant for clinical outcomes. Indeed, the agonism at 5-HT1A receptors, shared by different compounds, as well as the antagonism at 5-HT7 receptors may provide additional properties, as demonstrated by the recent experience with lurasidone [49,50].

5-HT7 and 5-HT1A receptors are abundantly expressed in the hippocampus (HIP) and amygdala, limbic areas that are strongly implicated in anxiety and mood disorders [51,52]. Both 5-HT7 blockade and 5-HT1A agonism are able to ameliorate phencyclidine-induced learning and working memory deficits, suggesting a procognitive action [53,54]. Furthermore, these properties may mediate antidepressant-like and anxiolytic actions, as well as neuroplasticity effects that are beneficial for long-term changes [55–57].

3.3. Acetylcholine receptors

A peculiar feature of clozapine action profile is the agonistic activity at α7 nicotinic acetylcholine (α7nACh) receptor, which may ameliorate spatial learning and recognition memory [58,59]. Clozapine has been found to normalize auditory gating in a dose-dependent manner precisely through α7nACh receptor [60–62], thus improving sustained attention abilities. Garzòn and colleagues recently demonstrated that α7nACh and D2R co-localize within some mesocorticolimbic dopamine neurons, both at somatic and dendritic synaptic level, suggesting that these receptors are mutually engaged in the control of ventral tegmental area (VTA) outputs [63]. Thus, simultaneous blockade of D2R and activation of α7nACh receptors may account for the superior therapeutic effectiveness of clozapine above other APs [63].

With regard to muscarinic receptors (AchMR), activation of the AchM1R and AchM4R seems to mediate procognitive effects [64]. N-desmethyl-clozapine, a clozapine metabolite, has been suggested to exert its action by acting as a partial agonist at AchM1R [65,66]. Noteworthy, novel compounds acting as positive allosteric modulators of AchM4R have been found to reverse amphetamine-induced and ketamine-induced abnormalities [67,68]. Xanomeline, a selective AchM1R-M4R agonist demonstrated meaningful clinical improvements in schizophrenia in a recent double-blind, randomized, multicenter phase II trial [69]. On these bases, Karuna Therapeutics developed a co-formulation of xanomeline and trospium chloride, the latter being an approved muscarinic antagonist that does not meaningfully cross the blood-brain barrier, in order to preferentially stimulate central AchMRs and avoid peripheral cholinergic adverse events [70]. In addition, a new selective allosteric modulator of AchM4R, CVL-231, has recently been developed. In fact, CVL-231 successfully passed a phase Ib trial, demonstrating clinically relevant antipsychotic activity and a well-tolerated profile in patients suffering from schizophrenia [71]. AchM1R-M4R agonism may therefore represent a novel striking mechanism of action for APs, which is not present in the vast majority of marketed APs.

3.4. Histamine receptors

APs can display an anxiolytic and hypnotic effect also by antagonizing the histamine H1 receptor, as is the case of clozapine, olanzapine, risperidone, quetiapine [72,73]. Nonetheless, H1 antagonism has been identified as a main cause of APs-induced weight gain, appetite-promoting and metabolic side effects [74]. Since polymorphisms of the histamine receptor H4 have been found to predict risperidone efficacy, this receptor has been thought to contribute to the APs mechanism of action [75].

3.5. Adrenergic receptors

Several atypical APs (i.e., olanzapine, quetiapine, clozapine, risperidone, aripiprazole) also block the norepinephrine alpha receptors [76–79]. α1 receptor blockade may contribute to the suppression of positive symptoms by reducing striatal hyperdopaminergia, while α2 adrenoreceptor antagonism (mainly exhibited by clozapine and risperidone) may account for ameliorating effects in subjects affected by negative, depressive, and cognitive symptoms by improving dopaminergic functions in the PFC [76]. The role of α2a and α2c subtypes receptors in neurocognition has not yet been clarified. However, it has been argued that α2a receptor blockade may be detrimental for cognitive functioning, while α2c receptor blockade exerts beneficial effects [80,81]. Of interest, iloperidone and quetiapine display the highest α2c/α2a receptor selectivity; clozapine has an affinity three times higher for α2c than for α2a receptors and the highest D2/α2c receptor ratio among APs tested [82].

3.6. Glutamate receptors

Glutamate has been strongly involved in schizophrenia pathophysiology and an N-methyl-D-aspartate (NMDA) hypofunction has been postulated [83–86]. Since reduced NMDAR activity on inhibitory GABAergic neurons leads to disinhibition of downstream glutamatergic neurons, targeting the group II/III metabotropic glutamate receptor (mGluR-II/III) has been considered a strategy to treat schizophrenia symptoms by normalizing glutamate alterations [87–90]. For instance, clozapine may exert a modulatory role on glutamate excess in the thalamocortical pathway. In addition, lumateperone may indirectly act on glutamate transmission via its effect on D1R, resulting in increases in NMDAR as well as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) currents [91].

A complementary approach to increase NMDAR coactivation by inhibiting glycine transporter 1 (Fig. 1) has been abandoned after the failure of bitopertin in a phase III trial [92–94].

The weak NMDAR antagonist AVP-786, the deuterated form of

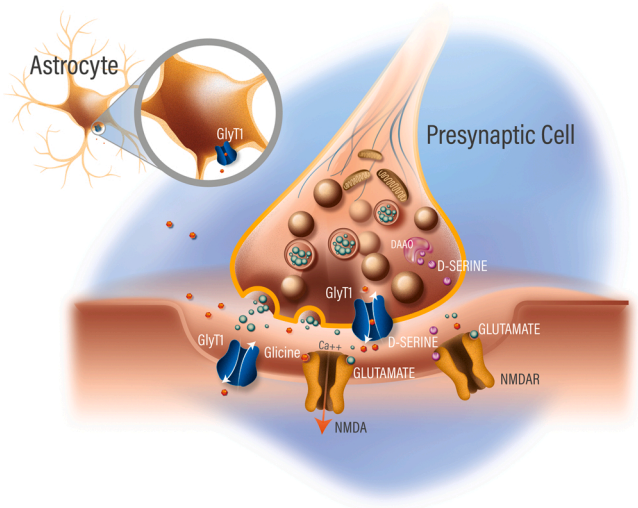

Fig. 1. Novel potential targets of antipsychotics. GlyT1 is responsible for removing glycine from the synaptic cleft and transporting it within astrocytic cells. According to the NMDAR hypofunction hypothesis of schizophrenia, enhancing glycine levels by inhibiting GlyT1 may improve NMDAR activity and, in turn, prove to be useful in schizophrenia. Another potential approach to mitigate NMDAR hypofunction may be the inhibition of the enzyme DAO, responsible for D-serine degradation. When DAO is inactivated, D-serine levels increase in the synaptic cleft and produce effects consistent with increased NMDAR functioning. GlyT1: Glycine Receptor Transporter 1; NMDAR: N-Methyl-D-aspartate receptors; DAO: D-amino acid oxidase.

dextromethorphan, is being tested for the treatment of negative symptoms of schizophrenia [95,96]. In fact, the recent approval of esketamine for treatment-resistant depression opened new scenarios involving the testing of novel glutamatergic modulators even for negative symptoms of schizophrenia. As we may imagine, the main concern regarding the use in schizophrenia patients of an NMDAR antagonist, albeit weak, is the possibility of a re-exacerbation of positive symptoms [97].

3.7. Opioid receptors

Samidorphan, an antagonist at μ-opioid receptor (Ki = 0.052 nM) and a partial agonist at κ and δ-opioid receptors, was previously investigated for the treatment of craving, addiction, and depression [98]. It has recently attracted attention as part of the combination product Alkermes (olanzapine + samidorphan) developed for the treatment of schizophrenia and bipolar I disorder. In fact, samidorphan can mitigate the cardiometabolic negative effects and weight gain induced by olanzapine alone [99].

The development of other opioid modulators for psychiatric disorders has perhaps been limited due to their abuse potential. However, despite the paucity of studies, a recent meta-analysis suggests the effectiveness of opioid antagonists either as adjunctive treatment to standard therapy or monotherapy [100], encouraging future studies for treating positive and negative symptoms of schizophrenia.

4. Intracellular receptors

4.1. Sigma receptors

Sigma receptors (σR) were first identified as a subtype of opioid receptors, until they were recognized as a separate class of receptors located in the endoplasmic reticulum membranes, and characterized by promiscuous ligand binding [101].

Since σRs are implicated in the modulation of NMDAR activity [102], targeting σR has been proposed as a viable strategy for the treatment of schizophrenia [103]. Several psychotropic agents show a certain degree of affinity for σ_1 receptors, including haloperidol, but also fluvoxamine, sertraline, ketamine, and others [104,105]. Dextromethorphan, tested as add-on treatment in schizophrenia patients, also behaves as an agonist at σ_1 sites [106]. Lastly, pimavanserin, an antipsychotic molecule that does not bind to D2R and recently approved for the treatment of Parkinson's psychosis, has a low affinity for σ_1 receptors (Ki = 120 nM).

4.2. Trace amine-associated receptors 1

Trace amine-associated receptor 1 (TAAR1) acts as a modulator of monoaminergic transmission with a predominantly intracellular expression, largely distributed throughout the monoaminergic systems [107–109]. TAAR1 regulates catecholamine release and affects synaptic plasticity. Knocked-out animals for the gene encoding TAAR1 displayed abnormalities in NMDAR functioning in prefrontal [110] and schizophrenia-like endophenotype [111]. On the other hand, TAAR1 agonist compounds have been found to reverse hyperlocomotion induced by stimulants or NMDAR antagonists [112]. Pharmacological manipulation of TAAR1 has shown interesting implications for mood homeostasis [113] and cognitive functioning [114–116]. The new investigational antipsychotic compound SEP-363856, which does not occupy D2R, shows distinctive agonist activity at TAAR1 and 5-HT1A receptors, without binding D2R, and it appears to have a prominent ability to modulate the functional activity of the PFC [117]. This compound, equipped with an innovative mechanism of action, displays a favorable safety profile and has been found effective either on positive and negative symptoms of schizophrenia [118].

5. Enzyme inhibition

A quite innovative and interesting mechanism of action for APs involves enzyme inhibition. For instance, the inhibition of D-amino acid oxidase (DAAO), which is the enzyme responsible for D-serine degradation, may result in a net increase of this D-amino acid acting as a dynamic gatekeeper of NMDAR (Fig. 1) [119,120]. Despite the promising preclinical results on DAAO inhibitors [121], findings from clinical trials in patients suffering from schizophrenia are still inconclusive. In particular, sodium benzoate is currently being tested in the phase IIb/III trial [122], whereas luvadaxistat (NBI-1065844) failed to meet its primary endpoint in the phase II INTERACT study [123].

6. Blockade of monoamine transporters

It has recently been demonstrated that atypical APs may act as monoamine transporter (i.e., dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET)) inhibitors.

Of interest, the clinical efficacy of APs generally declines with long-term treatment, although D2R blockade remains fairly stable. Recently, APs have been shown to robustly suppress DAT expression in the VTA and substantia nigra pars compacta at the initial stage of treatment, as well as to reduce the readily releasable vesicular pool [124]. Therefore, instead of D2 antagonism, it has been proposed that the clinical efficacy of AP therapy may be attributed to adaptations of DAT and inhibition of vesicular dopamine release, which are temporary and do not persist in long-term treatment. From this point of view, the later emergence of treatment resistance may be independent of D2R upregulation and involve the reinstating of baseline abnormal conditions of DAT activity and dopamine release [124].

With regard to serotonin reuptake, Lumateperone, which has been recently approved by the FDA for the treatment of schizophrenia, exhibits a significant binding to SERT (62 nM Ki), which may contribute to antidepressant activity [125].

Moreover, norepinephrine (NE) activity at alpha-adrenoreceptors in the locus coeruleus has been involved in depressed mood, fatigue,

difficulty concentrating [125]. It is noteworthy that the main metabolite of quetiapine, norquetiapine, displays a high affinity for NET, acting *de facto* as an antidepressant drug, in line with the clinical profile of quetiapine on bipolar depression [126].

7. Mechanisms related to the chemical structure of APs

Some actions of APs cannot be solely attributed to their receptor profile, but may originate from the chemical structure of the molecule. For example, weak-base APs such as clozapine and haloperidol may accumulate in the central nervous system (CNS), within endosomes or synaptic vesicles, thus creating an enriched pool of APs ready to be released [127]. When released in the synaptic cleft, APs inhibit voltage-gated sodium and calcium channels, with subsequent reduced release of other synaptic vesicles containing the neurotransmitter [128]. In other words, weak-base agents exert an autoinhibitory presynaptic effect which contributes to the overall APs action.

On the other hand, lipophilic APs may accumulate nearby the membranes or inside the cell. Hence, their concentrations remain high at D2R post-synaptic sites where are sequestered, resulting in long-lasting antagonism regardless of dissociation constants and specific binding kinetics [129].

8. Neuroprotective effects

8.1. APs exert neuroprotective effects by increasing BDNF expression

Schizophrenia is characterized by impaired plasticity and reduced expression of neurotrophic molecules promoting growth, survival and differentiation of neurons [130,131]. APs may counteract such alterations and exert neuroprotective effects by upregulating the levels of trophic factors, including brain-derived neurotrophic factor (BDNF) (Fig. 2) and nerve growth factor (NGF).

A meta-analysis by Fernandes et al. including 41 studies has suggested that peripheral BDNF levels are positively correlated with AP treatment, regardless of the clinical response [132].

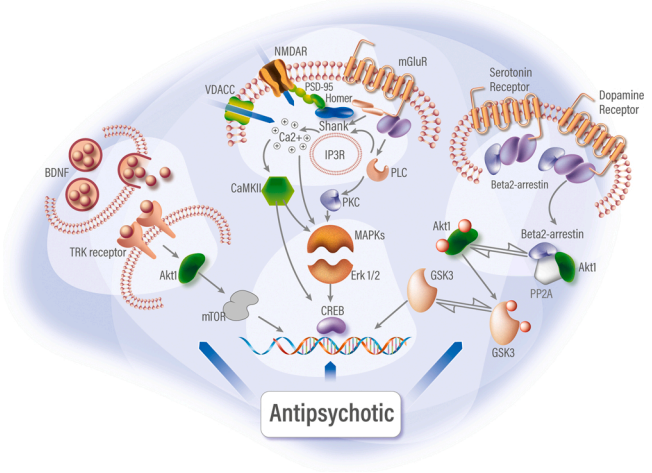

Fig. 2. Intracellular mechanisms in the action of APs. APs may modulate different signaling mechanisms downstream from synaptic changes, including MAPK/ERK and Akt/GSK3 pathways. In addition, APs upregulate BDNF that activates its downstream TrkB/Akt/mTor pathway. Each of these intracellular signaling cascades may converge on CREB, a transcription factor that leads to the expression of several genes involved in proliferation, differentiation, survival, neurogenesis, and neuronal plasticity. BDNF: Brain derived neurotrophic factor; TrkB: tropomyosin related kinase. mTor: mammalian target of rapamycin; NMDAR: N-Methyl-D-aspartate receptors; MAPK: mitogen-activated protein kinase; ERK: extracellular signal-regulated kinase; GSK3: Glycogen synthase kinase 3 beta; CREB: cAMP-response element binding protein.

Chronic administration of clozapine, olanzapine, and lurasidone increased BDNF expression in the HIP, while haloperidol was associated with a reduction [133–135]. Injection of MK801, which is associated with schizophrenia-like dysfunction, decreases BDNF levels in the HIP [136], which were restored by acute and sub-chronic treatments with risperidone [136,137]. Sub-chronic aripiprazole treatment has been found to increase BDNF expression in rat substantia nigra [138,139]. More in general, atypical APs have a greater propensity to induce BDNF expression, when compared to typical APs [140]. However, chronic exposure to risperidone and quetiapine has also been reported to result in an increase in the proBDNF/BDNF ratio [141,142]. Similarly, chronic clozapine treatment was also associated with decreased BDNF in mPFC [143]. Therefore, the effects of APs on BDNF release seem to depend on the dose and duration of treatment [144], rather than the class to which they belong. Moreover, the modulation of BDNF may also depend upon the experimental paradigm as well as the brain region investigated. For example, chronic lurasidone treatment is able to normalize the expression of BDNF within the PFC in a preclinical model of chronic stress exposure during adulthood, an effect that is associated with the ability of this AP to improve the anhedonic phenotype of stressed rats [145]. Similarly, a sub-chronic lurasidone treatment during late adolescence was able to prevent the reduction in BDNF expression in the PFC of animals exposed to prenatal stress, whereas the up-regulation of the neurotrophin following lurasidone administration was more prominent in the dorsal HIP of mice exposed to prenatal immune challenge [146,147].

8.2. APs promote neurogenesis

APs may also promote neurogenesis, a process that is often altered in schizophrenia and that may also represent a proxy of plasticity. It has been argued that APs ability to promote neurogenesis may mediate the beneficial effects of these agents at a clinical level, especially to target cognitive symptoms [148–150]. For instance, clozapine is able to prevent neurogenesis impairment induced by NMDAR antagonists [151,152] or chronic mild stress [149]. On the other hand, chlorpromazine showed a depressive effect on the early phase of rat subventricular zone neurogenesis [153].

Moreover, low doses of atypical APs seem to be more effective compared to both high doses of atypical APs or low doses of typical APs on hippocampal neurogenesis [154]. However, even with low doses of atypical APs, the newly generated cells do not survive and are subsequently not integrated into the existing hippocampal circuitry, suggesting that neuronal survival is unaffected by chronic AP treatment [154].

8.3. The effects of APs on myelination

Neuroinflammation may precede white and gray matter pathology, due to axonal degeneration, myelin breakdown, reduced density of astroglia and oligodendroglia. Demyelinating or dysmyelinating axons, apoptotic oligodendroglia, vacuolated or swollen astroglia, and reactive microglia may disturb the synchronization between brain regions and lead to structural and functional dysconnectivity, which has been frequently reported in schizophrenia [155].

Diffusor tensor imaging studies allow the evaluation of myelin integrity, white matter structural parameters, and the effect of AP treatment. A popular study by Garver et al. showed that patients who responded to APs had restored myelin integrity compared to drug-free patients or those who did not respond well [156].

A common way to investigate potential APs protective effects against demyelination is to re-assess myelin status after cuprizone challenge (which determines demyelination and oligodendrocyte apoptosis) and AP treatment [157]. Several studies pointed to the peculiar ability of quetiapine to exert supportive effects for oligodendrocyte differentiation or regeneration, as well as myelin repair, by preserving the survival of

mature oligodendrocytes and accelerating the maturation of oligodendrocyte precursors [158–161]. These effects appear to be mediated by the Notch pathway, which acts as a regulator of oligodendrocyte precursors, cell specification, and myelination processes [160,162,163]. Quetiapine has demonstrated not only the ability to promote remyelination and restore the Notch pathway but also to attenuate white matter abnormalities in cuprizone-challenged animals [164,165]. Further reports indicate that also other atypical APs such as clozapine and olanzapine, may attenuate myelin breakdown and protect against white matter damage, but this does not apply to haloperidol [166–168].

9. Immediate-early gene modulation by APs

Membrane receptors targeted by APs activate multiple intracellular downstream signal transduction pathways, with a subsequent variety of final effects mediated by second messengers. Glutamatergic post-receptor events are also crucially regulated by postsynaptic density (PSD), acting as a physical and functional mesh containing ionotropic and metabotropic glutamate receptors, ion channels, and signal molecules [169]. In order to appropriately converge on nuclear targets (i.e., transcription factors including c-fos, c-jun, arc, homer, and others), these cascades involve several specific effectors which phosphorylate a large number of substrates, namely kinases (e.g., CAMK, MAPKs, PKA etc.) (Fig. 2).

The impact of APs on gene expression seems to follow a peculiar regional specificity and topographical pattern, depending on their characteristics and the degree of D2R blockade. For instance, typical APs activate c-fos expression primarily in striatal regions, while clozapine induces c-fos in the cortex but does not have an effect on the striatum [170,171]. Moreover, haloperidol has been found to induce robust expression of several immediate early genes (IEGs) including Arc, c-fos, Zif-268, Norbin, and Homer throughout the entire striatum, whereas amisulpride is selective for the limbic system [172]. In this vein, increased functional inter-thalamic connectivity [173], as well as connectivity between caudate-putamen subdivisions [174], has recently been reported with an IEG-based network approach after exposure to haloperidol, possibly indicating the propensity of this AP to induce the emergence of motor side effects. On the other hand, novel APs such as aripiprazole, lurasidone, and blonanserin significantly increased the expression of Arc in the dorsal HIP [175–178], a brain region relevant for learning and memory processes. An acute administration of the novel compound SEP-36385, an agonist at serotonin 5-HT1A and TAAR1 receptors, is able to increase IEGs expression in the PFC and, to a lesser extent, in the ventral HIP [117]. The anatomical specificity of gene expression modulation exerted by these agents may therefore underlie distinctive clinical features such as the proposed antidepressant and pro-cognitive effects.

Besides the magnitude of D2R antagonism, the duration of the treatment may also affect IEG expression. For instance, Homer1a appears to be more robustly induced by acute treatment rather than chronic, regardless of the specific receptor binding profile [179]. This may probably explain the emergence of the so-called ‘tolerance’ or loss of efficacy in long-term treatment.

In summary, APs actions extend far beyond synaptic mechanisms, through the modulation of intracellular mechanisms that converge [180,181] onto the modulation of IEG expression. The temporal or spatial transcriptome fingerprint profile of APs is and will be essential to understand the molecular mechanism underlying the uniqueness in regulating brain mechanisms [182].

10. AP effects on synaptic plasticity

One of the most striking effects of APs that have emerged in the last decade of clinical research is the impact on brain volumetry and morphology [183] detected by different in vivo imaging methods. This challenging and controversial issue parallels in a relevant translational perspective the preclinical findings, in vivo and in vitro, showing that AP treatment can affect the core of synaptic architecture, modify the shape of the dendritic spine, and modulate the expression of genes at specialized structures of the synapse such as the PSD.

10.1. AP effects on dendritic spines

Dendritic spines are the pivotal units of brain circuits, which contact and establish the most excitatory synapses. The tip of dendritic spines contains a disk-shaped structure, detectable by electron microscopy: the PSD [184]. It has been considered a structural and functional “lego” [185], responsible for integrating and propagating signal transduction into specific intracellular compartments and effectors. The size and shape of the dendritic spine, as well as the composition of PSD, are deranged in postmortem brains from schizophrenia patients [186–188], and the administration of APs can affect the shape and molecular composition of the dendritic spine. Therefore, it is important to disentangle the impact of APs on synaptic components by means of in vivo and in vitro modeling. APs differentially modulate the shape and number of dendritic spines via the activation of AKT-GSK-3β cascade (Fig. 2) [189]. For instance, low doses of clozapine and aripiprazole, as well as high doses of aripiprazole, have been found to increase the number of spines, the levels of PSD95, phosphorylated Akt, glycogen synthase kinase-3 (GSK-3β). On the other hand, high-dose clozapine and haloperidol at both dosages result in opposing effects [189].

The Neonatal Ventral Hippocampal Neonatal Lesion is a highly replicated model of schizophrenia [190], associated with significant alterations of dendritic arborization, dendritic spine density, and dendritic spine shape [191]. Of interest, risperidone administration counterbalanced the pathomorphology and behavioral changes induce by Neonatal Ventral Hippocampal Neonatal Lesion [192].

10.2. APs and the postsynaptic density

Converging evidence indicates that APs can significantly impact the expression of glutamatergic postsynaptic genes [170,193–197]. Therefore, it is possible that some synaptic changes elicited by APs administration could be associated, at least in part, with the modulation of the gene expression and functioning of adapter, scaffolding, and signal transducer proteins within the PSD [170,196]. APs can not only induce differential changes in the expression of PSD genes (i.e., Homers vs PSD 95 vs Shank) but differentially affect even the expression of splicing forms of the same gene (Homer1a vs Homer1b/c), capturing the complexity and the value of their orchestrated interaction for the architecture of the glutamatergic synapse [198–200]. For instance, acute and chronic haloperidol exposure have different effects on the expression of Homer and Shank; moreover, the two isoforms of Homer, Homer1a and Homer1b/c, are frequently modulated in different direction (relative increase vs decrease) [198,201].

PSD gene expression may be differentially influenced by AP treatment depending on the receptor profile, the dose and duration of the treatment [179]. A paradigmatic example is given by the effect on Homer1a by acute administration of increasing doses of haloperidol. Homer1a is initially induced in the caudate-putamen, a well-known topographic target of D2R antagonists, but it is also progressively induced in other regions of the brain where lower doses do not show any detectable change [200]. Taken together, these observations allow making some inferences regarding the role of APs receptor profile on PSD gene expression modulation. For example, the prevalent expression of Homer1a in the cortex elicited by asenapine and the prevalent expression of the same gene in the striatum after acute administration of haloperidol have been hypothesized to be related to the different relative ratio of D2R and D1R occupancy of the two drugs [200]. Regarding the role of different dopaminergic receptor subtypes, experiments performed with selective compounds have shown that the modulation of D2R receptors is the main player in regulating PSD gene expression

[199].

Furthermore, the duration of treatment can significantly impact the effects of APs on PSD gene expression. For example, acute or chronic exposure to haloperidol can cause different changes in the cortex and striatum in Homer1a and Homer1b/c [202]. A differential effect of APs on gene transcripts of PSD proteins has been detected when the APs are administered in naïve vs. pre-treated rats, with modifications of the ratio between Homer1a/Homer1b transcripts and differential effects in cortex and striatum [203].

In summary, multiple and converging findings demonstrate that APs may significantly impact the structure and function of dendritic spines and PSD proteins' gene expression in a distinctive way depending on the receptor profile, duration, and dose of treatment.

11. Epigenetic effects and chromatin remodeling properties of APs

Common epigenetic modifications associated with schizophrenia-like phenotype include increased expression of DNA methyltransferase 1 (DNMT1) and ten-eleven methylcytosine dioxygenase-1 (TET1), as well as enrichment of 5-methylcytosine (5MC) and 5-hydroxymethylcytosine (5HMC) at promoters of genes involved in survival, neurotransmission, and synaptic plasticity [204,205]. It may be inferred that an appealing feature of APs may be the ability to regulate epigenetic mechanisms in order to normalize transcriptional alterations in subjects affected by schizophrenia [206,207]. According to recent evidence, APs can affect epigenetic homeostasis and influence the host methylome [208,209]. Against this background, clozapine has been regarded as the best "demethylating" agent, since it reduces the hypermethylation status of promoters of schizophrenia-related genes (for instance, GAD67, reelin, and BDNF), thus enhancing their transcription [210,211].

The ability to reverse the expression of genes downregulated in schizophrenia is not shared by other tested APs. It has been proposed that such feature may be a peculiarity of clozapine, possibly arising from its D1R antagonism [212]. However, epigenetic changes have also been reported with olanzapine, sulpiride, quetiapine, blonanserin, and limitedly with haloperidol [211,213–220]. Risperidone has been found to disassemble heterochromatin structures along the G-protein/AC/PKA pathway [221].

Modulation of miRNA can also represent an important epigenetic mechanism elicited by APs. As an example, miR-30a, a microRNA involved in the regulation of axon guidance and neurotrophin signaling, has been found dysregulated in several psychiatric disorders, such as schizophrenia and mood depression [222,223]. Noteworthy, sub-chronic treatment with lurasidone was able to prevent the upregulation of miR-30a in response to early life stress exposure [222]. Of interest, lurasidone treatment is also able to reverse long-lasting epigenetic changes associated with a depressive-like phenotype in stressed rats. Indeed, exposure to chronic mild stress is associated with a reduced expression of *Gadd*45β mRNA levels through a hypermethylation of its glucocorticoid responsive elements [224]. Lurasidone administration has been found to normalize DNA methylation status of stress-related genes, as well as their expression levels [224]. Thus, the modulatory activity observed on stress-related genes may account for the antidepressant action of lurasidone. A synergistic potentiating effect is played by valproic acid augmentation which is known to act as an inhibitor of the histone deacetylase (HDAC) enzyme [176,225].

12. APs on inflammatory and redox mechanisms

Schizophrenia has been conceptualized as an inflammatory disease in light of the stress-vulnerability-inflammation model [226]. Patients suffering from schizophrenia show alterations of the HPA axis, as well as increased pro-inflammatory cytokine expression, a T helper cells Th1/Th2 imbalance, microglia activation and other abnormalities of both innate and adaptive immune systems [227]. Different lines of evidence point to a close link and mutual interactions between neurotransmitter and immune systems [226,228]. On these bases, APs, acting on different neurotransmitter systems, may attenuate both the acute and prolonged inflammatory response [229,230].

12.1. APs modulate both innate and adaptive immunity

APs can exert an immunosuppressive action by modulating both innate and adaptive immune processes, probably by enhancing the Akt/PI3K pathway downstream the dopamine D2R. D2R antagonism activates Akt, which phosphorylates several intracellular substrates, including GSK -3β, leading to its inactivation (Fig. 2) [231].

Microglia are resident macrophage-like cells, the first-line of immune CNS defense, which remain in a quiescent state until activated by injury or infection [232]. Upon activation, microglia trigger the host immunological pathways, which can result in neuroinflammation, release of cytokines, production of microglia-derived free radicals, neuronal damage, and eventually cell death. PET studies using specific radioligands for the 18–kDa translocator protein evaluated reactive microglia in vivo [233], and found increased retention of the ligand in subjects affected by schizophrenia, proving evidence for an abnormal microglia activation in the early stage of the illness [234]. Noteworthy, resident microglia do not typically express D2R in the healthy brain, although brain injury may induce *de novo* D2R expression on activated microglia. Therefore, dopaminergic manipulation may modulate microglia functions during neuroinflammation [235]. For instance, replicated findings suggest that quetiapine, clozapine, amisulpride, and aripiprazole are capable of reducing microglia activation [236–239]. Moreover, the microglia activation status can strongly influence the APs effects also on cytokine balance, shifting toward the anti-inflammatory cytokine IL-10 as mentioned below [240].

APs may also modulate the function of Toll-like receptors (TLRs), which are implicated in innate immunity, through recognition of pathogen-associated molecular patterns. In fact, schizophrenia patients exhibit a greater extent of monocytes expressing TRL4, as compared to healthy subjects, an effect that is normalized by olanzapine and risperidone [241]. Similarly, recent studies report that also clozapine and paliperidone treatment significantly prevented TLR4 activation [241,242].

Likewise, stimulation of TLR3 may trigger the inflammatory cascade and the subsequent secretion of pro-inflammatory cytokines, eliciting oxidative and nitrosative stress. Paliperidone has shown a regulatory effect on TLR3 activation in a mouse model of schizophrenia [243].

Complement activity, another major component of the innate immune system, appears to be reduced by subchronic administration of haloperidol [244]. Furthermore, clozapine has been found to inhibit Th1 cell differentiation by reducing T-bet mRNA expression while enhancing GATA3 [245,246]. T-bet and GATA3 orchestrate the polarization of the immune response, being crucial for the differentiation of CD4+ T cells into Th1 or Th2 effector cells, respectively [247]. Haloperidol has also been shown to suppress the Th1 immune response in dendritic cells [248], although controversial reports [245]. Therefore, certain atypical Aps may determine an immunologic shift of Th1/Th2 balance, which may be harmful under infectious conditions, while at the same time beneficial in the event of an autoimmune disease characterized by Th1 excessive activity.

12.2. APs reduce the levels of mediators of inflammation

A "kindling" process of the immune system in schizophrenia patients may result from adverse events in early childhood, leading to immune disturbances in adult life, with increased neuroinflammatory response to minor challenges. Sustained neuroinflammation has been proposed to contribute to detrimental remodeling of brain architecture, and elevated cytokines in peripheral blood correlate with reduced cortical volume in patients with schizophrenia [249]. On the other hand, APs acting on a

variety of neurotransmitter receptors may alter the balance between pro- and anti- inflammatory signals [228,250]. Such effects may contribute to their beneficial clinical effects, particularly in the treatment of anhedonia and depressive symptoms [251].

Repeated noxae and infectious stimuli experienced in the early stage of development may affect the HPA axis, making it hyperactive. The HPA axis plays a crucial role in immunomodulation and, when activated, induces the release of glucocorticoids, capable of suppressing the inflammatory response, by modulating the expression of cytokines, chemokines, adhesion molecules, and inhibiting the functions of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) [252]. In this perspective, paliperidone has been found to rescue lipopolysaccharide (LPS)-induced HPA hyperactivity through the maintenance of the correct cytokine environment [253].

For instance, quetiapine and its metabolite norquetiapine both increased levels of the anti-inflammatory cytokine interleukin 10 and reduced levels of the pro-inflammatory cytokine interferon gamma (IFN-γ) in serum in acute inflammation models [254,255]. A similar pattern of gene expression was detected in brain regions such as the HIP and PFC [254]. Another study by Ko et al. showed that chronic quetiapine reduced peripheral levels of interleukin 1 beta (IL-1β), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and IFN-γ [256]. Under strong inflammatory stimuli, also clozapine, risperidone, and haloperidol have been found to reduce the levels of interleukin 1 alpha, IL-1β, interleukin 2, and interleukin 17 [257]. Aripiprazole and olanzapine exposure also decreased mRNA levels of IL-1β, IL-6, and TNF-α in peripheral blood mononuclear cells [258]. Nonetheless, it should be noted that the risk of developing metabolic syndrome is greater with clozapine and olanzapine than with other APs, suggesting that they may enhance inflammatory processes rather than alleviate them [259,260]. A recent study has solved this apparent paradox, demonstrating that olanzapine induces inflammatory cytokine reactions in peripheral tissues without affecting the CNS in rodents [261]. Therefore, chronic treatment with olanzapine may cause inflammatory-mediated metabolic disturbances with minimal or no adverse effects in the brain.

Lurasidone has been found to reverse the up-regulation of IL-1β induced by chronic mild stress [251]. Similarly, a study investigating a wide array of immune parameters, taking into account the levels of 40 different cytokines or chemokines, showed that risperidone administration leads to a condition of global immunosuppression in healthy mice [262], although the results of clinical studies are somewhat conflicting [263]. The anti-inflammatory effects of APs may depend on the inhibition of NLR family pyrin domain containing 3 (NLRP3) inflammasome, which is an intracellular sensor that detects a wide range of dangerous microbial or endogenous signals, leading to a pro-inflammatory state [257,264]. NF-kB plays a critical role in the activation of the inflammatory cascade and the differentiation of immune system cells [265]. APs may modulate NF-kb activity by inhibiting the inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ), which mediates nuclear translocation of the two subunits p65 and p50 of NF-kb and the subsequent induction of cytokine gene expression. Against this background, it is of interest that thioridazine has been recently repurposed by docking-based virtual screening as a promising anti-inflammatory drug acting as a selective inhibitor of IKKβ [266].

12.3. APs have antioxidant activity

Reactive microglia accounts for the production of microglia-derived free radicals, responsible for oxidative stress and neuronal damage. Oxidative stress has a detrimental effect on neuronal cells by modulating mitochondrial functions, epigenetic regulation, inflammatory responses, and neurotransmission [267].

Typical APs have been reported to worsen oxidant imbalance [268], whereas atypical compounds may be associated with antioxidant effects [269–271]. Indeed, typical APs might lead to increased lipid peroxidation, impaired antioxidant defense and subsequent neurodegeneration associated with the emergence of motor side effects [272].

For instance, paliperidone has been found to activate the nuclear factor erythroid-related factor 2 (NRF2) pathway in the brain, which results in the transcription of antioxidant enzymes [273]. Risperidone prevented schizophrenia-related oxidative stress by increasing the enzymatic activity of catalase (CAT) and superoxide dismutase (SOD) in several brain regions [274]. Quetiapine and aripiprazole also increased SOD1 activity in human erythrocytes in vitro [275]. Compared to other APs, pretreatment with haloperidol and risperidone showed the larger propensity to reduce the brain activity of hydrogen sulfide forming enzymes such as cystathionine-γ-lyase and cystathionine ß-synthase [276].

Furthermore, risperidone treatment has been associated with a reduction in lipid peroxidation in the PFC of an animal model of schizophrenia [192]. Similarly, quetiapine revealed a relevant protective effect against lipid peroxidation in human plasma [277,278], and has been found to normalize changes in oxidative parameters (i.e., CAT and glutathione peroxidase activity) after cuprizone exposure [159,279]. Clozapine and olanzapine displayed intracellular reactive oxygen species scavenger activity by reducing the formation of hydroxyl radicals and superoxide anions [280,281]. Since a negative correlation between brain antioxidant glutathione levels and the severity of negative symptoms has been found in schizophrenia patients, the antioxidant properties of APs may be of great relevance for their therapeutic effects, in particular for the subset of patients with prominent negative symptoms [282]. Dysregulated redox balance may also be involved in the emergence of depressive symptoms. For instance, the chronic mild stress model of depression is associated with oxidative stress and its detrimental effects on GABAergic parvalbumin positive neurons. Of interest, the effects of lurasidone in ameliorating the anhedonic phenotype in stressed rats may depend, at least in part, on its ability to restore parvalbumin expression through modulation of NRF2 in the dorsal HIP [146,283].

A similar effect on the imbalance of redox mechanisms in chronically stressed rats has also been shown for the AP drug blonanserin [175,176,284].

13. Brain structural and volumetric changes related to APs exposure

A progressive reduction in brain volume has been described in schizophrenia and, although considered due to an intrinsic pathological process [285], its association with both short-term and long-term AP treatments has been repeatedly reported [286–288]. Since mice lacking the D2R do not display neuroanatomical changes in response to APs administration, it has been proposed that these effects may be mediated by dopaminergic perturbations [289]. Given that D2R expression may be sparse in one brain region and abundant in another, volumetric changes may be complex and heterogeneous in schizophrenia patients. Beyond D2R occupancy, the peculiar metabolic profile of APs can also influence the degree of brain structural changes. In fact, APs that, among others, induce consistent impairments in lipid metabolism may seriously affect cortical myelination, which in turn may be responsible for alteration of cortical thickness [290]. Patients suffering from schizophrenia often undergo long-term treatment, and many confounding effects such as aging and duration of the illness come into play, making it difficult to dissect the specific effect of APs on changes in the volume of gray and white matter. Among other variables, the cumulative dose of APs has been correlated with reductions in cerebral volume in the majority studies [181,286,291].

Based on their distinctive features, APs may differentially impact the volume and structures of the CNS. A large study conducted by the "Enhancing Neuro Imaging Genetics Through Meta Analysis Schizophrenia" working group showed that cortical thickness is reduced to a greater extent in patients on typical APs, as compared to atypical ones [292]. Moreover, remodeling effects may be regionally distinct. For instance, typical APs have been reported to affect total and frontal gray

matter, while atypical APs preferentially affect lower frontal, parietal, and caudate volume [293]. On the other hand, when focusing on white matter, atypical APs were associated with larger volumes of parietal white matter [293] and appear to exert a protective effect [294,295]. Although other gray matter structures were found to be reduced after APs exposure, the volume of the basal ganglia appears to increase bilaterally [296–298]. This finding is more frequent with typical APs, and goes along with the reported increased cerebral blood flow within striatal regions after acute administration of neuroleptics [299].

However, it remains to be clarified whether APs-related volume reduction in schizophrenia patients correlates with clinical worsening or deterioration [249, 300–303]. Given the inconsistency of the results, it is possible that parameters other than thickness (i.e., neocortical surface area) may represent more reliable indicators of cognitive performance and symptomatologic improvement [304]. Nonetheless, it should be emphasized that clozapine-related thalamo-striatal volumetric reduction [305], as well as cortical thinning seem to predict better clinical outcomes, and improvements in cognitive symptoms [306]. It cannot be excluded that changes in brain structures induced by APs may be the expression of resilient re-adaptive mechanisms rather than neurotoxicity processes. Therefore, functional imaging studies may help to better understand the structure-function relationship and the APs action on the connectivity of the brain network.

14. APs effects on functional connectivity

As a result of the impaired synaptic efficacy, schizophrenia is also characterized by altered cortical-subcortical connectivity, as proposed by the "dysconnection hypothesis" [307]. Several studies attempted to investigate connectivity changes with AP treatment by functional magnetic resonance imaging (fMRI) or PET. Based on the complexity of their receptor profiles, AP treatment can result in both increases and decreases of neural activity in a region-specific manner [308–311]. AP response appears to be mediated by the restoration of VTA/midbrain connectivity to bilateral regions of the thalamus [312], as well as by the normalization of thalamocortical activity [313–315], insular subdivisions [316] and the hippocampal connectivity [317,318]. Moreover, clinical improvements have been associated with increased functional activation of the PFC [319], the cingulate gyrus in the default mode network [320], the inferior parietal lobule in the executive control network [321], and interconnectivity between the anterior cingulate cortex and putamen in the frontostriatal network [322,323].

APs belonging to different classes do not display common effects on blood-oxygen-level-dependent (BOLD) signal, depending on the affinity for the D2R [324]. Ettinger et al. showed that patient receiving atypical APs showed a left prefrontal BOLD signal increase in response to working memory load, whereas typical APs were associated with BOLD decrease in this area [325]. Furthermore, the switch from typical to atypical APs has been associated with increased procedural learning-related activation in the superior and inferior frontal gyrus, anterior cingulate cortex, and caudate-putamen [326]. On the other hand, an fMRI study investigating the acute effect of aripiprazole and haloperidol administration in healthy volunteers revealed no significant differences in frontal cortex activation between the two drugs during a task targeting executive functioning [327]. The same research group explored the effect of these two typical APs on mesolimbic activity: haloperidol exposure was associated with a diminished activity in the ventral striatum, while the aripiprazole response was similar to placebo [328]. Increased activation of the dopaminergic mesolimbic system may lead to the aberrant assignment of salience to neutral stimuli, which is a key feature of schizophrenia pathophysiology. In this perspective, haloperidol ability to reduce mesolimbic activity and possibly induce indifference to salient stimuli could be interpreted as a guarantee of greater effectiveness on positive symptoms. While action on the ventral striatum mediates the effects on positive symptoms, connectivity in dorsal striatum predicts the improvement in negative symptoms [329]. It has been proposed that APs may reduce salience attribution either to pleasant or negatively-valenced stimuli, by reducing the activation of the ventral striatum and anterior cingulate cortex to positive stimuli, as well as the activation of the orbitofrontal cortex and the insula to aversive stimuli, respectively [330]. Nonetheless, the ventral striatum response during reward prediction was reduced only in patients treated with typical APs, but not with atypicals, highlighting the fact that atypical APs may show a favorable clinical profile for negative symptoms [331,332]. In addition, by comparing the effects of D2R partial agonists to other atypical APs, the former compounds were associated with increased activation of the dorsolateral PFC during working memory tasks, while the latter reduced the recruitment of this region [333].

FMRI studies highlighted the effects of certain APs on controlling impulsivity and violent behavior. For instance, quetiapine has been found to modulate functional connectivity between amygdala and PFC in patients during exposure to scenes of virtual aggression, thus suggesting an anti-aggressive effect [334]. Brexpiprazole reduced BOLD activation in the right ventrolateral PFC during tasks associated with control of impulsivity, supporting the hypothesis that brexpiprazole may prevent harmful behaviors in schizophrenia patients [335].

8-week treatment with quetiapine extended-release resulted in increased resting-state connectivity of the amygdala, associated with a noticeable antidepressant and anxiolytic effect [336]. Moreover, amisulpride treatment decreases resting state connectivity between the nucleus accumbens and subgenual anterior cingulate cortex, similar to the effects detected in patients receiving the noradrenaline reuptake inhibitor reboxetine [337]. Since pathological hyperconnectivity between these regions has been detected in depression, decreased activity observed with amisulpride may contribute to its antidepressant effect [336].

AP treatment may modulate discrete parameters and state statistics of the network, such as measures of functional integration and segregation, small-world organization properties [174,338,339], and dwell time values [340] of brain networks.

In summary, functional connectivity studies allow us to better understand the mechanism of action of APs, considering changes in whole brain activity and adopting a network-based perspective that may integrate the complexity of their modulatory activity on multiple neurotransmitter systems.

15. APs restore abnormalities in gamma oscillations

Synchronized oscillatory activity in the gamma frequency range (30–100 Hz) is critical for efficient cognitive processing and functional brain network connectivity. Gamma band oscillations have been found to be largely perturbed and unstable in schizophrenia (enhanced or reduced), reflecting the difficulty in integrating information from distant brain regions, correlating with positive symptoms and cognitive impairment [341]. Increased gamma activity in schizophrenia patients has been hypothesized to represent an adaptive mechanism to cope with progressive loss of cortical gray matter [342]. APs may normalize disturbed gamma oscillations and be beneficial for neural network functioning [343]. For instance, olanzapine, clozapine, and risperidone restored abnormalities in cortical network oscillations induced by either amphetamine or phencyclidine [343], each exhibiting a distinctive electroencephalogram fingerprint. Studies investigating the gamma-influencing effects of APs showed that haloperidol and clozapine have the highest inhibiting potential [344–348]. Since D3R has been involved in the regulation of gamma activity [344], APs with preferential D3R binding may exert procognitive effects by ameliorating the coherence and synchronization of gamma circuits [27,349]. Although the biological role of D4R in the treatment of schizophrenia has not yet been clarified, D4R manipulations are effective in modulating gamma oscillations in vitro [44], and this mechanism may perhaps underlie clozapine's ability to improve decreased network

functions. Finally, both mGlu2/3 receptor agonists have shown the ability to normalize gamma activity in rodents challenged with ketamine [348,350].

16. Discussion: final remarks and overall critical appraisal

The precise mechanism of action and the multiple effects of APs remain not completely understood almost seventy years after the introduction of this class of drugs. Despite this caveat, several lines of evidence both at the preclinical and clinical level have unveiled a set of multimodal mechanisms of AP action. Findings and limitations in disentangling the multimodal action of these compounds can be summarized as below.

1. The protean manifestation of psychosis and the complexity of the APs' receptor profile compel delimiting the symptoms targeted by APs to disentangle the most relevant mechanisms of action in terms of efficacy. There is no doubt that despite the multiple effects of APs, the efficacy against positive symptoms remains the key one and, in this regard, the action at dopamine D2R is indubitably the most relevant [351,352].
2. The concept of dopamine D2R "occupancy" should be preferred to the one of "blockade" [353] in the light of the mechanism of actions of the available partial agonists (aripiprazole, brexpiprazole, and cariprazine). Moreover, some of these compounds (i.e., aripiprazole) may also functional selectivity with the modulation of different transduction signaling pathways [17,354].
3. The modulation of the serotonergic system appears to be quite relevant for different clinical features, from the low liability of atypical APs to induce extrapyramidal side effects (5-HT2A antagonism) to the potential effects on depressive symptoms and cognition (5-HT1A, 5-HT6 and 5-HT7), although some of these effects may be driven by the regulation of neurotransmitter release in specific brain regions [49,355].
4. The modulation of muscarinic receptors by APs is facing an exciting time with the Xanomeline-Trospium combination that has passed clinical phase II [69]. If further steps in clinical trials will confirm the efficacy and a good tolerability profile of these compounds, we may have a game-changing treatment.
5. *In vivo* and in vitro preclinical studies have shown significant effects of APs on the structure of the synapse and in the architecture of dendritic spines [193], which may depend on the anatomical selective activation of intracellular signaling leading to the induction of discrete changes in gene transcription (i.e., c-fos, Arc, Homer) [170,175,182,356]. Such changes are, at least in part, mirrored by the structural and functional change detected in imaging studies in patients, suggesting their potential role in clinical outcomes.

Despite advances in understanding the molecular effect of acute and chronic APs administration and the envision of novel molecules exploiting innovative targets [117], several caveats are still unresolved.

First, it should be acknowledged that even if several intracellular mechanisms elicited by antipsychotic exposure have been unveiled, these mechanisms are not coincident by default with the AP outcome. Second, the specific etiology of psychiatric disorders in which APs have an approved indication, (i.e., schizophrenia, psychosis, bipolar disorders, and depression, the last one in augmentation), as well as the precise pathophysiology of discrete symptoms, remains to be fully understood.

Third, the receptor profile as well as the molecular signature for each APs are strongly dependent on their clinical dose. Therefore, with the increase of the dose, it is conceivable that different receptors, downstream mechanisms, and brain regions will be recruited, which will ultimately affect the circuits involved in specific disease symptoms [179,200,357–359].

Fourth, APs effects on brain morphology, functional activity and brain connectivity, supported by multiple imaging findings, are disparate, heterogeneous a correct interpretation is not straightforward [363–365].

However, it should be acknowledged that the predictive and explanatory value of these findings in terms of AP mechanism of action is still at the beginning, and needs to be refined with more data from multimodal, larger, and polycentric studies before being applied to real-world antipsychotic treatment [366].

These considerations highlight the need for a better understanding of schizophrenia neurobiology, as well as of the molecular mechanisms of APs, in order to define a road-map for the development of new therapeutic strategies based on the identification of novel molecular targets and biomarkers that will possibly target the pathologic domains for which the available antipsychotics have limited efficacy.

Role of the funding source

The editorial and publication work has been realized thank to an unconditional support of Angelini Pharma.

CRediT authorship contribution statement

Andrea de Bartolomeis: Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Supervision. **Annarita Barone:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Veronica Begni:** Writing – original draft, Writing – review & editing. **Marco Andrea Riva:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

Declaration of interest

M.A.R. has received compensation as speaker/consultant from Angelini, Iqvia, Lundbeck, Otzuka, Sumitomo Dainippon Pharma and Sunovion, and he has received research grants from Lundbeck, Sumitomo Dainippon Pharma and Sunovion. A.dB. has received research support from Lundbeck, Otsuka, Janssen Italy, Pfizer, lecture fees from Takeda, Sunovion, Lundbeck Chiesi, Mylan-Vitria, Roche, Angelini. He has served as a consultant in advisor boards and/or scientific writing for Otsuka, Jansen, Lundbeck, Roche, Eli Lilly, Takeda, Recordati, Iqvia, Mylan-Vitria, Angelini, Ethos.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2022.106078.

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