Clozapine for Treating Treatment-Resistant Schizophrenia

Subjects: Neurosciences

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Clozapine is listed as one of the most effective antipsychotics and has been approved for treating treatment-resistant schizophrenia (TRS); however, several type A and B adverse reactions, including weight gain, metabolic complications, cardiotoxicity, convulsions, and discontinuation syndromes, exist. The critical mechanisms of clinical efficacy for schizophrenia, TRS, and adverse reactions of clozapine have not been elucidated. The GABA isomer L-β-aminoisobutyric acid (L-BAIBA), a protective myokine in the peripheral organs, was identified as a candidate novel transmission modulator in the central nervous system (CNS). L-BAIBA activates adenosine monophosphate-activated protein kinase (AMPK) signalling in both the peripheral organs and CNS. Activated AMPK signalling in peripheral organs is an established major target for treating insulin-resistant diabetes, whereas activated AMPK signalling in the hypothalamus contributes to the pathophysiology of weight gain and metabolic disturbances. Clozapine increases L-BAIBA synthesis in the hypothalamus. In addition, the various functions of L-BAIBA in the CNS have been elucidated, including as an activator of GABA-B and group-III metabotropic glutamate (III-mGlu) receptors. Considering the expressions of GABA-B and III-mGlu receptors (localised in the presynaptic regions), the activation of GABA-B and III-mGlu receptors can explain the distinct therapeutic advantages of clozapine in schizophrenia or TRS associated with N-methyl-D-aspartate (NMDA) receptor disturbance compared with other atypical antipsychotics via the inhibition of the persistent tonic hyperactivation of thalamocortical glutamatergic transmission in the prefrontal cortex. L-BAIBA has also been identified as a gliotransmitter, and a detailed exploration of the function of L-BAIBA in tripartite synaptic transmission can further elucidate the pathophysiology of effectiveness for treating TRS and/or specific adverse reactions of clozapine.

clozapine L-β-aminoisobutyric acid | treatment-resistant schizophrenia | metabolic complication | thalamocortical pathway

1. Introduction

Traditionally, more than 30% of patients with schizophrenia spectrum are considered to suffer from treatment-resistant schizophrenia (TRS) [1][2][3]. Clozapine is evaluated as the most effective antipsychotic agent for TRS since 30–60% of patients with TRS respond to clozapine medication [4][5][6]. Therefore, clozapine is currently the only approved antipsychotic for TRS treatment [7]. In fact, several guidelines recommend initiating treatment with clozapine for patients with TRS [8][9][10]. Furthermore, systematic reviews and meta-analyses have demonstrated that clozapine is associated with lower hospitalisation rates, lower overall discontinuation rates, and better overall symptom outcomes compared with other atypical antipsychotics [11][12][13].

All antipsychotics approved for the treatment of schizophrenia are antagonists of the dopamine D2 receptor at therapeutically relevant concentrations [14][15]. The introduction of clozapine in the 1970s marked a significant turning point in the pharmacotherapy of schizophrenia. As an alternative, clozapine minimised the risk of extrapyramidal symptoms, such as antipsychotic-induced parkinsonism and tardive dyskinesia, while demonstrating excellent efficacy for both positive and negative symptoms of schizophrenia [16][17]. Based on these clinical advantages of clozapine, receptor-binding profile screenings have contributed to the development of several second-generation antipsychotics (atypical antipsychotics) that share pharmacological characteristics distinct from the preceding first-generation antipsychotics (typical antipsychotics) [16][18]. It is well known that olanzapine has a similar receptor-binding profile to clozapine, except for the 5-HT7 receptor [19]; however, the specific effectiveness of clozapine for treating TRS suggests the pathophysiology of clozapine may involve molecules other than monoamine receptors.

Most atypical antipsychotics had been developed by exploring molecules that have similar receptor-binding profiles to clozapine that are distinct from the preceding typical antipsychotics, such as having a relatively lower binding affinity to the dopamine D2 receptor and higher affinity to serotonin 5-HT2A receptors [20]. Therefore, the pathophysiological hypothesis proposed to distinguish between typical and atypical antipsychotics, having a relatively low affinity to the D2 receptor and relatively high affinity to the 5-HT2A receptor, cannot account for the distinct therapeutic advantages of clozapine against other atypical antipsychotics.

Clozapine (CLZ), lurasidone (LUR), aripiprazole (APZ), brexpiprazole (Brex), olanzapine (OLZ), quetiapine (QTP), risperidone (RIS), zotepine (ZTP), and haloperidol (HPD) against serotonin (5-HT) type 1A (5-HT1A), type 2A (5-HT2A), type 2C (5-

HT2C), and type 7 (5-HT7) receptors, histamine H1 (H1) receptor, and dopamine receptors type 1 (D1) and 2 (D2). Data are equilibrium constant (Ki) values (nM).

2. Clozapine-Induced Metabolic Complications

Weight gain is the most prevalent adverse reaction of atypical antipsychotic medications. Weight gain induced by atypical antipsychotics usually occurs during the early stages of antipsychotic treatment (within the first year), with an increase of 7% over baseline weight observed in approximately two-thirds of antipsychotic-treated patients [21][22]. Diabetes treatment in patients treated with clozapine is manageable by following current diabetes treatment guidelines [23][24]. Thus, a history of diabetes in TRS patients does not constitute a contraindication to clozapine medication [25]. Among pharmacological interventions, metformin has an excellent safety profile and is the most effective for weight gain stabilisation [26][27][28]. Topiramate has also been demonstrated to be as effective as metformin in suppressive effects on clozapine-induced weight gain [29][30]. Glucagon-like peptide-1 (GLP1) receptor agonists have been recently shown to effectively mitigate clozapine-induced metabolic disturbances [31]. However, weight gain induced by antipsychotics other than clozapine, including olanzapine and quetiapine, reaches a plateau within the therapeutic dose range, whereas the unique features of weight gain with clozapine indicate a linear dose-dependent manner ranging from therapeutic to supratherapeutic doses [32]. This specific linear dose-dependent weight gain induced by clozapine indicates that different mechanisms might underlie the weight gain induced by other antipsychotics.

Atypical antipsychotic-induced metabolic complications have been considered to be related to the inhibition of the histamine H1 and serotonin 5-HT2A receptors, which leads to the disturbance of energy regulation systems in the hypothalamus [33][34]. The inhibition of the H1 and 5-HT2A receptors suppresses the synthesis of inositol trisphosphate (IP3), which activates the calcium-induced calcium-releasing system (CICR) via the enhancement of the IP3 receptor (**Figure 1**) [35][36]. The elevation in intracellular calcium ion levels activates adenosine triphosphate (ATP) synthase, leading to an increase in ATP and/or a decrease in adenosine monophosphate (AMP) levels (**Figure 1**) [34][36][37]. Therefore, CICR suppression induced by H1 and 5-HT2A receptor inhibition secondarily increases intracellular AMP levels, leading to the activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK) (**Figure 1**) [33][34][37][38]. This hypothesis has been supported by the clinical findings on high-affinity H1 and 5-HT2A receptor antagonistic antipsychotics, including zotepine, quetiapine, olanzapine, and clozapine listed as being high-risk for metabolic complications [32]. However, the activation of AMPK in the peripheral organs is one of the major therapeutic targets for insulin-resistant diabetes [28][39][40], whereas the activation of AMPK signalling in the hypothalamus increases feeding and reduces energy expenditure in the body [40].

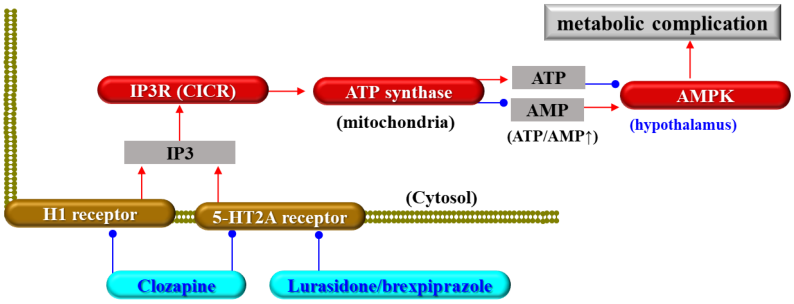

Figure 1. Schematic presentation of hypothalamic signalling associated with traditional hypothesis regarding the mechanisms of antipsychotic-induced metabolic complications and weight gain. Red and blue arrows indicate activation and inhibition, respectively. Abbreviations: H1 receptor—histamine H1 receptor, 5-HT2A receptor—serotonin 5-HT2A receptor, IP3—of inositol trisphosphate, CICR—Ca^{2+}-induced Ca^{2+}-releasing system, ATP—adenosine triphosphate, AMP—adenosine monophosphate, and AMPK—AMP-activated protein kinase.

Chronic administration of therapeutically relevant doses of clozapine, quetiapine, brexpiprazole, and lurasidone decreased IP3 synthesis, and increased AMP levels in the rat hypothalamus [38][41][42]. However, contrary to expectations, AMPK signallings were activated and unaffected by high-risk (clozapine and quetiapine) and low-risk (brexpiprazole and lurasidone) antipsychotics for weight gain, respectively [38][41][43][44][45]. Both clozapine and quetiapine are high-affinity antagonists of the histamine H1 receptor and the 5-HT2A receptor, whereas brexpiprazole and lurasidone are high-affinity 5-HT2A receptors but have low binding affinity to the H1 receptor [33][46]. Therefore, enhanced intra-hypothalamic AMPK signalling plays fundamental roles in antipsychotic-induced metabolic complications and weight gain, but decreasing IP3 with increasing AMP levels via inhibition of H1 and/or 5-HT2A receptors alone cannot explain the pathophysiology of antipsychotic-induced weight gain. Similar to clozapine, an H1 and 5-HT2A high-affinity atypical antipsychotic agent, olanzapine, which was established to also be a high-risk antipsychotic for weight gain, decreased IP3 synthesis [47][48]; however, olanzapine has been reported to enhance [34][49][50] and suppress [51][52] hypothalamic AMPK signalling with contradictory results.

3. Clozapine and TRS

3.1. Efficacy of Clozapine in TRS

TRS is internationally defined by the Treatment Response and Resistance in Psychosis (TRRIP) Working Group and includes the following aspects: the presence of persistent symptoms—including positive and negative symptoms, and cognitive impairment—over at least 12 weeks of at least moderate severity caused by moderate levels of functional impairments [53]. Symptom classifications and thresholds should be based on standardised and validated clinical rating scales. Insufficient response to medication with at least two different antipsychotic medications, with a minimum treatment duration of twelve weeks (six weeks for each antipsychotic agent). This corresponds to a minimum dose equivalent to 600 mg per day of chlorpromazine. Confirmation of adequate treatment adherence is defined as the patient having taken at least 80% of the prescribed dose. To achieve this, at least two methods should be employed, including counting tablets, patient and caregiver reports, and review of medical records and documentation. Additionally, plasma drug concentrations should be monitored at least once for each antipsychotic agent [53][54].

Incontrovertible evidence supports the superior efficacy of clozapine compared with other atypical antipsychotics in improving positive symptoms and global psychopathology in TRS [5][13][55][56]. Considering the lack of evidence to support using polypharmacy of antipsychotics other than clozapine that is as effective as clozapine, the efficacy of clozapine in TRS is evaluated as being more robust [57]. Furthermore, patients treated with clozapine have also shown improvements in treatment adherence, resulting in decreased rehospitalisation rates [57][58].

3.2. Candidate Pathophysiology of TRS

Some research groups have emphasised the importance of distinguishing between primary and secondary TRS: primary TRS already presents with antipsychotic-resistant clinical features at the onset of the schizophrenia spectrum, whereas secondary TRS develops at later stages of the schizophrenia spectrum after an initial adequate response to antipsychotics [59][60][61]. Dopaminergic supersensitivity induced by consecutive exposure to antipsychotics has been speculated as a candidate mechanism of secondary TRS [62]. Persistent exposure to antipsychotics upregulates postsynaptic D2 receptors, leading to further psychotic exacerbation [62]. The estimated overall response rate to antipsychotic medications ranges from 40% to 60% [63][64]. The response rate to antipsychotic medication in antipsychotic-naïve patients is estimated to be approximately 75%; however, the response rate in a second trial using antipsychotic medications other than clozapine was considerably lower, ranging from 20% to 45% [65][66]. Response rates to clozapine have been reported to be maximally up to 80% when treatment is initiated within the first 2–3 years after resistance is established [64][65][67]. With subsequent initiation of clozapine medication, the response rate might be as low as 30% [64]. The efficacy of clozapine against TRS is significant compared with other antipsychotics but decreases depending on the duration of antipsychotic exposure, which is similar to other antipsychotics. These clinical findings regarding duration-dependent resistance at least partially support the dopaminergic supersensitivity hypothesis [62].

The specific features of clozapine, such as low affinity and rapid dissociation from D2 receptors, are considered to be candidate mechanisms via which clozapine-induced D2 receptor supersensitivity is less than that of other antipsychotics [20][46][68][69][70]. However, several line studies have demonstrated that the dissociation rate of clozapine from D2 receptors is not significantly faster compared with the rates of other antipsychotics, such as quetiapine, amisulpride, remoxipride, and sulpiride [20][71][72][73]. These pharmacodynamic findings suggest that the efficacy of clozapine in secondary TRS cannot be solely explained by either its low affinity or rapid dissociation from D2 receptors, even if the pathophysiology of TRS involves D2 receptor supersensitivity.

3.3. Candidate Targets of Clozapine Other Than Monoamine Receptors

Although schizophrenia is commonly speculated to be a pathophysiologically contiguous spectrum between treatment-responsive schizophrenia and TRS, several findings suggest that TRS might be a subtype with extreme characteristics from the perspective of neurodevelopmental disorders [74][75]. In other words, there are possibly two subtypes of pathophysiology of TRS, one being secondary treatment resistance due to long-term exposure to antipsychotic drugs, and the other already developing as TRS during the onset period. Approximately 70–80% of patients with TRS have been reported to present antipsychotic-resistant clinical features from the first episode [74][75]. Furthermore, predictors of antipsychotic resistance in schizophrenia are similar to the clinical features of ‘neurodevelopmental’ schizophrenia, such as being male, being of a younger age at onset, poor premorbid adjustment, and a longer duration of untreated illness [76][77]. So far, various studies have revealed impairments in cognitive components, such as sensorimotor function, attention, working memory, visuospatial processing, verbal intelligence, and memory in TRS patients compared with treatment-responsive schizophrenia [78][79][80][81]. These cognitive impairments are more suggestive of impaired function of glutamate transmission (via thalamocortical pathways) than monoamine transmission (via the mesolimbic and mesocortical systems). These cognitive impairment

features of TRS suggest it may be caused by dysfunction of glutamatergic transmission (via thalamocortical pathways) rather than monoaminergic transmission (via mesolimbic and mesocortical pathways) [15][43][68][82][83][84][85].

Quantitative reviews of mRNA and protein expression of N-methyl-D-aspartate glutamate receptor (NMDA-R) in post-mortem studies have demonstrated that both mRNA and protein expression of the NR1 subunit of NMDA-R in the prefrontal cortex decreased in patients with schizophrenia compared with healthy volunteers [86]. mGluR5 (I-mGluR) signalling in the dorsolateral prefrontal cortex decreased, indicating that NMDA-R hypofunctions [87]. In the post-mortem frontal cortex of untreated patients with schizophrenia, downregulation of group II metabotropic glutamate receptors (II-mGluR), such as mGlu2/3, was reported [88]. Conversely, III-mGlu receptor expression in schizophrenia remains unreported, whereas the activation of the III-mGlu receptor suppressed the hyperactivated transmission induced by NMDA-R impairment in wild-type and II-mGluR deficit models [83][89].

In other line studies, both post-mortem and experimental animal model studies also demonstrated that impairment of the GABA-B receptor plays an important role in the pathophysiology of schizophrenia. Decreased GABA-B receptor expression in the hippocampus, prefrontal cortex, inferior temporal cortex, and entorhinal cortex in schizophrenia has been reported [90][91]. Decreased GABA-B receptor expression in the prefrontal cortex and hippocampus of the DBA/2J schizophrenia model compared with C57BL/6J mice was also revealed [92]. Clinically, clozapine is evaluated as the most effective antipsychotic to improve sensorimotor gating dysfunction in patients with schizophrenia [93]. Maladaptive perseveration with strategies that cannot lead to the desired outcome resulting from cognitive and behavioural inflexibility via possible sensorimotor gating dysfunction in the thalamocortical pathway is considered a characteristic feature of schizophrenia [33][46][68][94][95]. Pre-pulse inhibition (PPI) has been established as an endo-phenotype of sensorimotor gating function. Clozapine improved PPI deficits in an experimental animal model, ZFP804A mutant mice, and an NMDA/glutamate receptor (ketamine)-induced model [96][97]. Baclofen has also been indicated to counter PPI disruption of the acoustic startle reflex produced by the blockading of the NMDA-R [92]. Notably, the effects of baclofen on PPI deficit were comparable to those of clozapine but more prominent than those of the typical antipsychotic, haloperidol [92]. These behavioural studies suggest that the impacts of a GABA-B deficit contribute to sensorimotor impairment in schizophrenia.

A recent study using molecular docking calculations for the X-ray crystal structure of the GABA-B receptor suggested that clozapine, like baclofen, might bind to the GABA-B receptor [98]. Both clinical and preclinical studies have suggested that clozapine enhances GABA-B receptor function, and the direct binding of clozapine to the GABA-B receptor has not been demonstrated but, rather, has been denied [32][99][100]. Considering these previous findings, the enhancement of GABA-B receptor function with clozapine may be mediated by an indirect mechanism of clozapine rather than a direct agonist action. Therefore, the hypothesis regarding the stimulatory effects of clozapine on GABA-B receptor function is intriguing for understanding the underlying pathophysiology of the clinical efficacy of clozapine in TRS.

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