

Repurposing antipsychotics as glioblastoma therapeutics: Potentials and challenges (Review)

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Abstract. Glioblastoma multiforme (GBM) is the most common and most lethal primary brain tumor, with tragically little therapeutic progress over the last 30 years. Surgery provides a modest benefit, and GBM cells are resistant to radiation and chemotherapy. Despite significant development of the molecularly targeting strategies, the clinical outcome of GBM patients remains dismal. The challenges inherent in developing effective GBM treatments have become increasingly clear, and include resistance to standard treatments, the blood-brain barrier, resistance of GBM stem-like cells, and the genetic complexity and molecular adaptability of GBM. Recent studies have collectively suggested that certain antipsychotics harbor antitumor effects and have potential utilities as anti-GBM therapeutics. In the present review, the anti-tumorigenic effects and putative mechanisms of antipsychotics, and the challenges for the potential use of antipsychotic drugs as anti-GBM therapeutics are reviewed.

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1. Introduction

Glioblastoma multiforme (GBM) is the most common and most malignant type of brain cancer. Despite extensive efforts over the past decades, the prognosis for GBM patients remains dismal. The median survival time of GBM patients is currently 14.6 months from diagnosis, which is only a few months longer compared with 30 years ago. The five-year overall survival rate of GBM is <10% (1). Currently, the standard-of-care for the majority of GBM patients is a combination of surgical resection, radiation and chemotherapy with temozolomide (TMZ) (2-4). However, this aggressive treatment provides only palliation.

There are several factors to limit clinical improvements against this devastating disease. First, molecularly targeted agents with demonstrated therapeutic benefits in other types of cancer have shown minimal or no efficacy against GBM (5). For example, bevacizumab, a neutralizing antibody against vascular endothelial growth factor, is effective in treating certain cancers, including metastatic colon cancer and non-small cell lung cancer (NSCLC). By contrast, recent large-scale clinical trials with bevacizumab have achieved no improvement in the overall survival of newly diagnosed GBM patients (6,7). Epidermal growth factor receptor (EGFR) is frequently activated in GBM, as 40-60% of GBM tumors have genomic amplifications and/or activating mutations of the *EGFR* gene. The first-generation small-molecule EGFR inhibitors, such as gefitinib, have performed poorly against GBM in several clinical trials (8-10). While the Bcr-Abl-targeting drug imatinib revealed notable efficacy for patients with chronic myeloid leukemia, clinical trials of imatinib in GBM have failed to demonstrate any therapeutic advantages (11-13). Finally, dasatinib, a platelet-derived growth factor and Src inhibitor failed to show benefit in recurrent GBM patients, either alone or in combination with bevacizumab (14).

The low distribution of systemically administrated chemotherapeutics within the brain represents a significant challenge in treating GBM. The blood-brain barrier (BBB) restricts delivery of therapeutic compounds, particularly for large molecules and hydrophilic drugs. The BBB can be compromised at the core of a GBM tumor, however, it is generally intact at the invading edges of the tumor. In addition, other

factors, such as a distinct immune system in the brain and interstitial pressure, limit the retention of drugs in the tumor. Concentrations of systemically administered antineoplastic drugs were reported to be significantly low in glioma tissues compared with blood (15). Thus, certain drugs that may otherwise be effective against GBM fail to show efficacy simply due to their low permeabilities or low retention capacities in the brain.

Recently, the strategies of utilizing the existing drugs for other diseases, known as 'drug repositioning' or 'drug repurposing,' have been extensively investigated as a method of drug discovery. The use of existing FDA-approved drugs can bypass or shorten critical steps of drug development, such as chemical optimization and toxicology testing, thereby resulting in a shorter time frame for clinical translation (16).

Antipsychotics deserve particular scrutiny as potential therapies for GBM. Antipsychotic drugs such as pimozide, *N*-methyl-D-aspartate receptor (NMDAR) agonists/antagonists, γ -aminobutyric acid inhibitors and valproic acids are frequently prescribed for the management of various psychiatric disorders, including schizophrenia, acute/chronic psychosis, delusional disorders, depression and anxiety disorder (17-20). These drugs have a long history of clinical use and tolerable safety in humans, and readily penetrate the BBB, which is particularly important for GBM (21). In the present review, an overview of various preclinical and clinical studies testing the efficacy of antipsychotics for the treatment of human malignancies, including GBM, is presented and the putative mechanisms for the anti-neoplastic actions of these antipsychotic drugs is reviewed.

2. Anti-neoplastic effects of antipsychotics

Antipsychotic drugs have been used for decades in various psychiatric clinical settings, and have tolerable or low toxicities and well-characterized profiles of sequelae. Due to the established safety of these drugs, combined with their proven ability to cross the BBB, antipsychotic medications are increasingly being tested for efficacy in patients with various cancers, including malignant brain tumors. Furthermore, epidemiological studies with diverse patient populations have reported significantly lower incidences of cancer among patients with schizophrenia compared with the general population (22-29). These findings support the possibility that antipsychotics may partially ameliorate the risk of cancer development, although molecular elucidations are yet to be accomplished.

Valproic acid has been approved for the treatment of psychiatric disorders such as bipolar disorder and schizophrenia. The anti-neoplastic properties of valproic acid have been demonstrated in leukemia and several solid tumors. One of the most well-studied molecular targets of valproic acid is the histone deacetylases (HDACs). Histone acetylation and deacetylation are epigenetic mechanisms that control gene expression via histone modification leading to the changes in chromatin structure. The overexpression and increased activity of HDACs have been reported in the stages of tumor initiation and progression (30-34).

Another antipsychotic drug that has shown encouraging results in several different types of cancer is pimozide. Pimozide has been used to treat psychiatric disorders for over

50 years. Pimozide inhibits the proliferation of breast cancer cells and significantly increases the sensitivity of tumor cells to γ -irradiation (35-37). The observed growth inhibition and radio-sensitization are believed to be due to inhibition of σ -receptors, which are atypical G protein-coupled receptors (GPCRs). Additionally, pimozide has been shown to exhibit promising activity in patients with metastatic melanoma (38). Pimozide also inhibits the activity of a deubiquitination complex, ubiquitin-specific protease 1 (USP1)/USP-associated factor 1 (39).

In addition, a number of psychiatric drugs have shown promising results in pre-clinical studies, although they have not yet demonstrated efficacy in human clinical trials. For example, the antipsychotic drug thioridazine selectively impaired the *in vivo* tumorigenicity of neoplastic pluripotent stem cells (40). It was reported that several antipsychotics, including phenothiazines, have anti-proliferative properties against various tumor cell lines, including neuroblastoma, non-small cell lung cancer, glioma and melanoma, which indicates that antipsychotics may be useful for adjuvant chemotherapeutic regimens (41). Drori *et al* showed that antipsychotics such as reserpine notably potentiated taxol- or anthracycline-associated cytotoxicity in human nasopharyngeal carcinoma cells (42). In another study, Haloperidol, a typical antipsychotic drug, augmented the cytotoxic effect of vinblastine, idarubicin and cisplatin in vinblastine-resistant human leukemia cells (43).

Wiklund *et al* tested the anticancer properties of six antipsychotics: Reserpine, chlorpromazine, haloperidol, pimozide, risperidone and olanzapine. All these drugs, with the exception of risperidone, showed selective growth inhibition of various cancer cell lines derived from lymphoblastoma, neuroblastoma, NSCLC and breast adenocarcinoma (44). In another multi-drug screening study, the antipsychotic drug class of the phenothiazines, consisting of chlorpromazine, levomepromazine, promethazine, trifluoperazine and thioridazine, displayed notable anti-proliferative and selective cytotoxic properties against various leukemia cell lines (45). Evidence to justify further investigation of drugs that modulate muscarinic receptor signals as anti-neoplastic therapies came from a recent study that examined the role of the autonomic nervous system (i.e. sympathetic and parasympathetic signals) in the development of cancer (46). The NMDAR pathway contributes to the pathogenesis of multiple human cancers, including pancreatic ductal carcinoma, breast cancer, ovarian cancer and glioma, and is associated with the poor prognosis of patients with those cancers. For example, MK-801, an NMDAR antagonist and potential antidepressant, displayed therapeutic efficacy in cultured cancer cells and tumor-bearing mice (47). In summary, a series of studies have reported the anti-tumorigenic effects of various antipsychotics, although further investigation is required to determine the precise molecular targets and mechanisms of these drugs.

3. Antipsychotics as anti-GBM therapeutics

Valproic acid was first tested 15 years ago to evaluate its efficacy against pediatric malignant gliomas (33). Since then, several studies have provided support to the hypothesis that valproic acid derivatives are a promising drug class for the treatment of GBM. Valproic acid attenuated the growth of

glioma cells by inhibiting angiogenesis (48) and inducing differentiation (49). In addition, valproic acid increased the sensitivity of glioma cells to conventional GBM therapies, including TMZ and γ -radiation (50,51).

As implied by its name, GBM harbors profound intra-tumoral heterogeneity. The cancer stem cell hypothesis posits the cellular hierarchy in which a subpopulation of highly tumorigenic, stem-like cells resides at the apex. While certain cancers may not follow cancer stem cell models, numerous studies support that the fact that the majority of GBMs harbor GBM stem-like cells (GSCs). GSCs share a number of characteristics with normal neural stem/progenitor cells, most notably a self-renewal capacity and potential for multi-lineage differentiation. As GSCs are enriched with tumor initiation/propagation capacities, and as they are phenotypically resistant to radiotherapy and chemotherapy, potential curative GBM therapies may require the targeting of GSCs, as well as the bulk of the tumor (52-61). Considering the cancer stem cell concept, Diamandis *et al* (62) screened 1,267 chemical compounds to identify molecules that inhibit the clonogenic growth of neural cells (59). Notably, several potent compounds were identified through this screen, including a number of dopamine receptor modulators (butaclamol, apomorphins and flupenthixol), an NMDA receptor antagonist (lifenprodil), an opioid receptor agonist (carbetapentane) and serotonin receptor agonists (62). Another chemical screening using embryonic stem cells and its derivative cancer cells showed that a dopamine receptor antagonist potently impaired the tumor formation capability of cancer stem cells (40). The phenothiazine class includes drugs such as thioridazine, fluphenazine or perphenazine, and is known to antagonize dopamine signaling. The anti-glioma effects of phenothiazines have been reported (63). Tricyclic neuroleptic drugs, such as chlorpromazine, promoted autophagic cell death in the PTEN-null U-87MG glioma cell line by inhibiting the PI3K/AKT/mTOR pathway (64). In addition, antipsychotics, such as paliperidone, pimozide and risperidone, which are selective 5-HT₇ inhibitors, have been studied for their potential use as an adjuvant chemotherapy in the management of GBM (65).

4. GPCR blockers in cancer

GPCRs transmit multiple biological signals through a heterotrimeric G protein associated with the inner surface of the plasma membrane (66). The heterotrimeric G proteins, which are composed of G α (G- α), G β (G- β) and G γ (G- γ) subunits, are bound to guanosine diphosphate (GDP) when they are inactive. Upon activation, GDP is replaced by guanosine triphosphate (GTP), resulting in subunit dissociation into a $\beta\gamma$ dimer and the GTP-bound α -monomer (67). The G α subunit is classified into four families: G α_s , G α_i , G α_q and G α_{12} . Each G α family can transmit different downstream signals, thereby affecting diverse biological functions (68). Despite the biological significance of GPCRs in tumorigenesis, selective GPCR-targeted anticancer drugs are few. The rarity of GPCRs as cancer therapies is rather striking considering that GPCRs are targeted by ~25% of top-selling drugs, including β -blockers, antipsychotics and analgesics (69). Typical antipsychotics, such as chlorpromazine and haloperidol, were

discovered in the 1950s. Although they are clinically effective, side-effects such as extrapyramidal symptom (EPS) and hyperprolactinemia have limited their chronic application. The more recently developed 'atypical' antipsychotics, such as clozapine, show comparable efficacy to the typical drugs, but without EPS (70,71).

The majority of antipsychotic drugs bind to dopamine receptors, antagonizing this signaling pathway in striatal cells (72). However, antipsychotics also have significant affinity for other GPCRs, including serotonin 5-HT_{1A}, α -adrenergic receptors and muscarinic receptors (73). Atypical antipsychotics regulate G $_i$ and G $_q$ activity by modulating the function of serotonergic 2AR and the G $_i$ -linked GPCR metabotropic glutamate 2 receptor heterodimeric complex (74). A cell-based functional assay to identify the pharmacological profile of 40 clinically useful antipsychotics revealed that almost all antipsychotics are potent inverse agonists of the 5-HT_{2A} receptor, a monoamine GPCR, as well as effective dopamine D2 receptor antagonists (75). A recent study demonstrated that clozapine and risperidone have activity at more than a dozen monoamine GPCRs (76). These findings collectively indicate that antipsychotics have high affinity and selectivity for GPCRs, but have low specificity among the GPCR superfamily.

Abnormal activation of GPCRs by unusually high levels of bio-active lipids, such as lysophosphatidic acid or sphingosine-1-phosphate, leads to expression of various cancer-associated genes involved in cell survival, proliferation, migration and angiogenesis (77-79). In addition, endothelin receptors, GPCRs that are upregulated in several types of cancer, regulate cell survival, angiogenesis, invasion, metastasis and epithelial-to-mesenchymal transition (80). Seven-transmembrane Frizzled family receptors and the co-receptor lipoprotein receptor-related protein are other GPCRs that initiate signaling within the canonical Wnt pathway, thus contributing to the development and progression of cancer (81-83). The Wnt/ β -catenin signaling pathway plays a crucial role in the development of GBM by promoting glioma proliferation, invasion and GSC formation (84-86). Hedgehog (Hh) signaling is another key component in the tumorigenesis of multiple malignancies (87,88). Smoothed (Smo), a seven-span transmembrane GPCR, is a key transducer of Hh signaling (89). Aberrant Hh pathway activation by the mutation of Smo is associated with the development of several cancers, including basal cell carcinoma and medulloblastoma (90). Ligand-dependent Hh pathway activation is involved in the tumorigenesis of gastrointestinal cancer, prostate tumors and glioma (91,92).

CXC chemokine receptors are another family of GPCRs that are indicated to be involved in tumorigenesis. Besides their roles in leukocyte chemotaxis, CXC chemokine receptors play an important role in cancer cell survival, proliferation and angiogenesis (93-96). The prominent expression of CXCR4, a G protein-coupled chemokine receptor, and its ligand, stromal cell-derived factor-1 α , result in the activation of MAPK and Akt, leading to enhanced survival in glioma cells (97). In addition, overexpressed CXCR4 is associated with an invasive phenotype in malignant glioma (98). Additionally, glioma stem-like cells promote angiogenesis via the CXCR4/CXCL12 signaling pathway (99).

Amongst the GPCRs, dopamine receptors are particularly notable target molecules for therapies aimed at cancer stem cells (40). Dopamine receptors are predominant in the central nervous system (CNS), and participate in various neurological processes, including motivation, cognition, memory and fine motor control (100). A recent study demonstrated that polymorphism of the dopamine receptor D2 is associated with the colorectal cancer risk, suggesting that an analogous situation could apply in CNS tumorigenesis (101). On the other hand, dopamine signaling enhances the efficacy of anticancer therapy in breast and colon cancer cell lines (102). In addition, the balance of peripheral dopamine signals is critical in tumor growth (103). Signaling via 5-HT₇, a relatively specific GPCR within the human nervous system, promotes the activation of extracellular signal-regulated kinases and STAT3, resulting in tumor survival and proliferation (65).

5. Conclusion

The dismal prognosis of GBM highlights the urgent requirement for the development of drugs with novel mechanisms of action. Of all the classes of drugs that affect brain function, antipsychotics have the longest history of clinical use, and comprise some of the most frequently prescribed drugs in the world. A growing body of evidence suggests that several antipsychotics display significant anti-neoplastic effects on multiple human cancers. For example, valproic acid attenuates cancer cell proliferation by inhibiting HDACs. Therefore, antipsychotic drugs may represent strong candidates for chemotherapeutic adjuvants in the treatment of GBM due to their clinically proven safety and accumulation in the brain, along with their anti-neoplastic efficacy.

One potential concern with the use of antipsychotics in cancer treatment is the possibility of unexpected adverse effects. Despite their long history of clinical application and a reliable safety profile, typical and atypical antipsychotics are known to cause a wide range of side-effects (104). The majority of antipsychotics induce CNS side-effects, such as sedation, headaches, dizziness and diarrhea in up to 50% of patients (105). More seriously, the extrapyramidal side-effects of typical antipsychotic drugs, including akathisia, dystonia and drug-induced secondary Parkinsonism, may prevent their chronic use (71). Second-generation atypical antipsychotics can also cause metabolic problems, such as obesity and type II diabetes (106). Thus, optimization of drug structures may be required to avoid adverse side-effects if the anti-tumorigenic effect of a given drug is proven.

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