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REVIEW

Glioblastoma chemotherapy adjunct via potent serotonin receptor-7 inhibition using currently marketed high-affinity antipsychotic medicines

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Glioblastoma treatment as now constituted offers increased survival measured in months over untreated patients. Because glioblastomas are active in synthesizing a bewildering variety of growth factors, a systematic approach to inhibiting these is being undertaken as treatment adjunct. The serotonin 7 receptor is commonly overexpressed in glioblastoma. Research documentation showing agonists at serotonin receptor 7 cause increased extracellular regulated kinase 1/2 activation, increased interleukin-6 synthesis, increased signal transducer and activator of transcription-3 activation, increased resistance to apoptosis and other growth enhancing changes in glioblastoma is reviewed in this paper. Because three drugs in wide use to treat thought disorders – paliperidone, pimozide and risperidone – are also potent and well-tolerated inhibitors at serotonin receptor 7, these drugs should be studied for growth factor deprivation in an adjunctive role in glioblastoma treatment.

Abbreviations
5-HT, serotonin; 5-HT$_7$, the serotonin receptor 7; cAMP, cyclic ademosine monophosphate; ERK1/2, extracellular regulated kinase 1/2; H$_1$, histamine receptor 1; IL-6, interleukin-6; STAT-3, signal transducer and activator of transcription-3; VEGF, vascular endothelial growth factor

Prelude

All the business of war,
and indeed all the business of life,
is to endeavor to find out
what you don't know by what you do . . .
Duke of Wellington, Arthur Wellesley 1769–1852 . . .

Introduction

Current glioblastoma treatment options offer limited extension of life over untreated disease course. Because humans are quite prone to madness that proclivity has resulted in much clinical and basic science research on the biochemical and neurophysiological underpinnings of the various forms of psychosis. That research in turn has given us neurophysiological insights that now are applicable to neuro-oncology. This short note reviews one such.

Our knowledge of the group of the 500 similar seven-transmenbrane non-olfactory receptors exceeds our clinical manipulation of these (Alexander *et al.*, 2009); this paper suggests a new use of one of these. Of these seven-transmenbrane receptors, about a dozen are recognized that have serotonin (5-HT) as the primary endogenous ligand (Alexander *et al.*, 2009).

Recent psychiatric research on neurotransmission at serotonin receptor 7 (5-HT$_7$) combined with

new understandings of the importance and mechanisms of glioblastoma's use of autocrine and paracrine growth stimulation paths suggest a new and currently available but unused glioblastoma treatment adjunct.

Of all drugs approved for use in humans currently in the EU and USA/Canada, the three exhibiting the most potent inhibition of 5-HT_7 are pimozide (Opler and Feinberg, 1991; Tueth and Cheong, 1993), paliperidone (Smith *et al.*, 2006; Marino and Caballero, 2008) and risperidone (Möller, 2005; Smith *et al.*, 2006). This paper will outline evidence for a glioblastoma growth stimulatory system stemming from agonism at 5-HT_7, suggesting that antagnonism by these three antipsychotic drugs may be of benefit. Unfortunately 5-HT_7 is only one of many growth stimulatory systems. Presumably all must be blocked for cure. Maybe this is a small start on that long path.

Serotonin receptor 7

One of several remarkable features of serotonin as a signalling molecule in brain function generally is that there are over a dozen currently recognized different receptors for it (Hannon and Hoyer, 2008; Alexander *et al.*, 2009). Each serotonin receptor has its own molecular structure, its own array of intracellular second messenger systems engaged, its own unique distribution pattern within brain regions and its own characteristic spatial distribution pattern on individual neurones and glia (Hannon and Hoyer, 2008). 5-HT_7 (reviewed in Thomas and Hagan, 2004) is of interest to neuro-oncology and is the subject of this paper because 5-HT_7 is the only serotonin receptor about which we have clear data showing activity in stimulating glioblastoma growth and three drugs used in psychiatry happen to potently inhibit it.

In the 16 years since its discovery, a large database on psychiatric effects of agonism or antagonism at 5-HT_7 has been generated (Roth *et al.*, 1994; Pittalà *et al.*, 2007; Hannon and Hoyer, 2008). Antidepressant activity of 5-HT_7 antagonism is suspected.

5-HT_7 like many other G-protein-coupled receptors is positively (Gs) coupled to adenylate cyclase (Hirst *et al.*, 1997; Thomas and Hagan, 2004; Pittalà *et al.*, 2007; Alexander *et al.*, 2009). Thereby agonists at 5-HT_7 increase intracellular cyclic adenosine monophosphate, cAMP.

5-HT_7 and GLIA

Two core research findings around which this note is built are that of Mahé *et al.* (2004) where all eight human glioblastoma cell lines tested expressed functioning 5-HT_7 (Mahé *et al.*, 2004) and that of Lieb *et al.* (2005) who documented 5-HT_7 on U373MG glioblastoma cell line where agonists stimulated extracellular regulated kinase 1/2 (ERK1/2) and interleukin-6 (IL-6) synthesis (Lieb *et al.*, 2005). This finding assumes particular importance given the prominent role of IL-6 in glioblastoma growth, as outlined below in the section on IL-6.

Taken alone the data of Mahé *et al.* (2004) and Lieb *et al.* (2005) would be weaker than it is. With supporting data below, their findings make inhibiting 5-HT_7 function an attractive target in adjunctive glioblastoma treatment. The various signalling paths discussed and documented in this paper that connect 5-HT_7 to growth enhancing changes in glioblastoma are depicted in Figure 1.

Extracellular regulated kinase 1/2 forms one of several signalling hubs through which diverse outer cell membrane receptors exert their effects. The critical role of ERK1/2 specifically in glioblastoma (Lopez-Gines *et al.*, 2008; Kim *et al.*, 2009) and the array of stimuli by which glioblastomas achieve a highly activated ERK1/2 state was reviewed in Lopez-Gines *et al.*, 2008; Kast, 2009; Samaras *et al.*, 2009; Zohrabian *et al.*, 2009.

Extracellular regulated kinase 1/2 is activated (phosphorylated) by 5-HT via activation of 5-HT_7 in monocytes (Soga *et al.*, 2007), T lymphocytes (Angileri *et al.*, 2008), microglia (Mahé *et al.*, 2004) and normal hippocampal neurones (Lin *et al.*, 2009). These findings compel us to test if 5-HT_7 agonism can/does stimulate ERK1/2 in human glioblastoma too.

Serotonin agonism at 5-HT_7 reduces monocytes' apoptosis rate *in vitro* and up-regulates the anti-apoptosis 26 kDa protein Bcl-2 (Soga *et al.*, 2007). Bcl-2 itself (Angileri *et al.*, 2008; Tagscherer *et al.*, 2008) and Bcl-2-related proteins (Stegh *et al.*, 2007; Degterev and Yuan, 2008; Stegh *et al.*, 2008; Yip and Reed, 2008) are up-regulated in glioblastomas and form one of several core anti-apoptosis changes in glioblastoma not seen in normal glia.

A caveat: the work of Lopez-Gines *et al.* (2008) showed that there are many paths to ERK1/2 activation that lead to apoptosis resistance and mitosis as shown in Figure 1, but also that there are paths active in glioblastoma obviating an obligatory ERK1/2 activation step (Lopez-Gines *et al.*, 2008). Many of the ERK1/2 activating paths that have been identified operating in glioblastoma are shown in

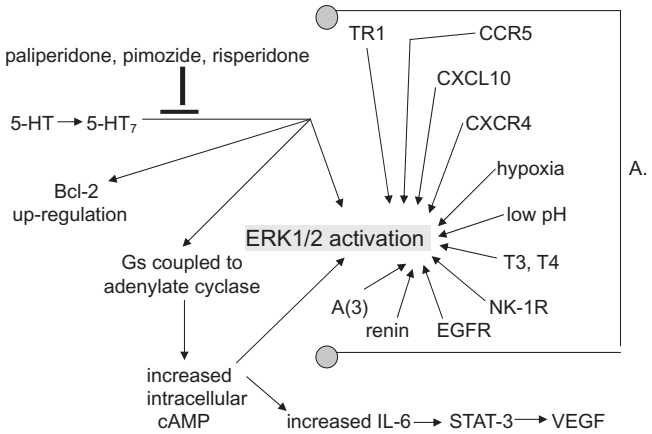

Figure 1

A schema drawn from data presented in text. Some of these relationships are putative, empirically demonstrated not causally established. For example it has not been shown that Bcl-2 up-regulation after 5-HT$_7$ ligation of serotonin is not secondary to adenylate cyclase activation, or to STAT-3 activation, or to ERK1/2 activation, or to none of these, or to some combination of these. Which of the three suggested drugs is best at 5-HT$_7$ signalling inhibition is unknown. Note the crowd of arrows pointing to ERK1/2 activation (phosphorylation). That's a problem. In all likelihood they can to at least some degree cross-cover for each other so that each of these and more must be inhibited for cure.

A. Some routes to ERK1/2 in glioblastoma. CCR5 is the chemokine receptor (synonomous with CD195) for RANTES (regulated upon activation, normal T-cell expressed and secreted, synonomous with CCL5). CXCL10 is the 10 kDa ligand for CXCR3. CXCR4 is the receptor for CXCL12. T3 is liothyronine, and T4 is levothyroxine. NK-1R is the receptor for the 11-amino-acid peptide neurotransmitter substance P. EGFR is epidermal growth factor receptor (synonomous with HER-1). A(3) is the adenosine receptor 3. TR1 is the transferring receptor 1. 5-HT, serotonin; 5-HT$_7$, the serotonin receptor 7; cAMP, cyclic ademosine monophosphate; ERK1/2, extracellular regulated kinase 1/2; IL-6, interleukin-6; STAT-3, signal transducer and activator of transcription-3; VEGF, vascular endothelial growth factor.

Condition or receptor system	References
CCR5	Kast (2010)
CXCL10	Maru *et al.* (2008)
CXCR4	Porcile *et al.* (2005)
Hypoxia	Kim *et al.* (2009)
Low pH	Xu *et al.* (2002)
T3, T4	Lin *et al.* (2009)
NK-1R	Kast (2009)
EGFR	Loew *et al.* (2009)
Renin/prorenin	Juillerat-Jeanneret *et al.* (2009)
A(3)	Gessi *et al.* (2010)
TR1	Calzolari *et al.* (2010)

Figure 1, with references in the legend but are not further discussed in text.

The drugs

Each drug has advantages and disadvantages. All three drugs are full antagonists, are fairly well tolerated with side effects that are readily reversible on discontinuation. Side effect reversibility might not hold for psychiatric patients taking these over decades but does hold true for the proposed use here as glioblastoma treatment adjunct.

Table 1 lists basic pharmacological parameters of the three drugs (Opler and Feinberg, 1991; Tueth and Cheong, 1993; Möller, 2005; Smith *et al.*, 2006). Common side effects are given below. All these drugs have a risk for the rare neuroleptic malignant syndrome. All three drugs have good safety margins when taken in overdose with suicidal intent. That safety margin allows clinical psychiatric practice not to use blood levels for titration. These drugs are dosed up or down by desired effect versus tolerability of side effects.

Although not potently so, all three drugs do have antinausea effects that can be helpful during standard chemotherapy. All side effects listed below are fully reversible on discontinuation or lowering of dose.

The three suggested 5-HT$_7$ antagonists are thought to exert their antipsychotic effects by a combination of antagonism at the dopamine-2 and the serotonin 2A receptors (Opler and Feinberg, 1991, Tueth and Cheong, 1993; Möller, 2005; Smith *et al.*, 2006). Metabolic disturbances such as weight gain, increased cholesterol and diminished glucose tolerance or frank diabetes tend to be seen after long-term use in psychiatric patients and are thought to result from antagonism at these receptors as well. Antagonism at alpha-adrenoceptors is mild and usually not clinically significant (Owens, 1994).

Pimozide advantages (Opler and Feinberg, 1991; Tueth and Cheong, 1993)

Pimozide has the highest affinity at 5-HT$_7$ of any marketed drug about which we have data. It is also the oldest. It is available as a generic drug, therefore potentially the cheapest.

Pimozide disadvantages

QTc prolongation is common but is not usually problematic in clinical practice but can rarely become so. Because of the risk of torsade de points and other arrhythmias increases with increased QTc, close monitoring of the QTc would be required if pimozide was used. Patients would best be shifted to

Table 1
All three drugs are eliminated by renal excretion

Drug	K_i (Nm)	$T_{1/2}$	Metabolism	Common blood levels in psychiatric patients ($ng \cdot mL^{-1}$)
Pimozide	0.5	2 days	3A4, 1A2	1–5
Risperidone	1.3	10–20 h	2D6	10–120
Paliperidone	1.3	1 day	none	10–120

K_i refers to drug affinity at serotonin receptor 7, 5-HT_7. $T_{1/2}$ is the circulating half-life. 3A4, 1A2 and 2D6 refer to hepatic P450 enzyme system responsible for primary catabolism of the drug.

an alternative 5-HT_7 inhibitor if prolongation exceeded 15% or 60 ms. Pimozide's inhibition at 5-HT_7 is reversible so potentially less potent at blocking 5-HT_7 signalling. Akathesia and parkinsonian signs and symptoms are common at higher doses. Prolactin elevation can be expected. Paucity of thought can occur.

Risperidone advantages (Möller, 2005)

Risperidone is now available as generic drug. Its interaction with 5-HT_7 is unusual in that inhibition of a given receptor is permanent for the life of that particular 5-HT_7 receptor (Smith *et al.*, 2006). Risperidone might covalently bind to 5-HT_7.

Risperidone disadvantages

Prolactin elevations are probably greatest with risperidone. Akathesia and parkinsonian signs and symptoms are common. Galactorrhea and paucity of thought can occur.

Paliperidone (=9-OH-risperidone, Invega®, Janssen Pharmaceuticals Inc., Titusville, NJ, USA)

Advantages (Marino and Caballero, 2008). Clinical experience in psychiatric patients indicates that paliperidone might be the easiest of these drugs for patients to tolerate. Paliperidone inhibition of a given receptor is permanent for the life of that particular 5-HT_7 receptor. This drug is the least likely to cause akathesia or parkinsonian problems. Oros® delivery system offers smoother blood levels.

Paliperidone disadvantages. Is still proprietary and by far the most expensive. As the newest we have least experience with it.

Each drug seems to have its advantage. Nothing will replace empirical testing. Although pimozide has higher affinity to 5-HT_7, risperidone and paliperidone even with slightly lower binding affinity might be more effective in inhibiting 5-HT_7 because of the unique irreversible nature of their interaction with 5-HT_7 (Smith *et al.*, 2006).

Parenthetical notes on the special nature of il-6

Data showing autocrine IL-6 mediated growth promotion of glioblastoma was first shown in 1997 and 1998 (Candi *et al.*, 1997; Goswami *et al.*, 1998). By different techniques using glioblastoma biopsy tissue, primary *ex vivo* culture, and *in vitro* glioblastoma cell lines, IL-6 continues to be shown to be an active growth promoting signalling system (Liu *et al.*, 2010).

Interleukin-6 is a 26 kDa multifunctional cytokine synthesized by many different cell types, of relevance here prominently so by monocyte lineage cells, glia and the cells and vasculature of glioblastoma as outlined and referenced below. The important role of IL-6 in glioblastoma growth was reviewed in 2006 with suggested drugs then to lower IL-6 signalling (Kast and Altschuler, 2006).

Evidence continues to accrue since then attesting to IL-6's role in glioblastoma's growth and determining some of glioblastoma's attributes. Lieb *et al.* (2005) documented that agonists at 5-HT_7 stimulated IL-6 synthesis and release from human glioblastoma cell line U373MG and in partial confirmation of the predictions of this paper; pimozide was shown to block this *in vitro* 5-HT_7-induced IL-6 increase (Lieb *et al.*, 2005).

In vitro exposure of microglia cell line MC-3 to serotonin also results in increased synthesis and secretion of IL-6 via agonism at 5-HT_7 (Mahé *et al.*, 2004). Fresh, primary resected human glioblastoma tissue has a disproportionatly high number of IL-6 receptors (Kudo *et al.*, 2009). Antibody to IL-6 receptors inhibited *in vitro* growth of U87MG glioblastoma cell line (Kudo *et al.*, 2009).

Glioblastoma patients' circulating monocytes are more active in IL-6 synthesis than are normal

monocytes (Samaras *et al.*, 2007; 2009). IL-6 driven up-regulation of vascular endothelial growth factor, VEGF, goes through a signal transducer and activator of transcription-3, STAT-3, mediated step (Loeffler *et al.*, 2005) leading to VEGF promoter's stimulation (Choi *et al.*, 2002; Brantley and Benveniste, 2008). In the glioblastoma cell line U-251 STAT-3 activation was shown to be secondary to autocrine IL-6 signalling (Rahaman *et al.*, 2002). STAT-3 is so uniformly up-regulated in glioblastoma tissue that it has been called a growth factor signalling hub (Brantley and Benveniste, 2008).

Resected glioblastoma tissue is strongly positive for IL-6 by immunohistochemistry (Samaras *et al.*, 2007; 2009) and ELISA on tissue homogenates (Choi *et al.*, 2002). Correspondingly high amplification of IL-6 gene was noted in half of surgical glioblastoma specimens (Tchirkov *et al.*, 2001; Samaras *et al.*, 2009), and that half has significantly shorter survival than did the non-amplified half (Tchirkov *et al.*, 2001; Samaras *et al.*, 2009). IL-6 gene amplification and protein overexpression was independently found also in half of cases examined (Sasaki *et al.*, 2001).

Independent concordant immunohistochemical documentation of increased IL-6 protein was seen in about half of all cases (Chang *et al.*, 2005) with average survival in that group of 7 months compared with 16 months in IL-6 immunohistochemical negative group (Chang *et al.*, 2005).

The direct relationship between intracellular cAMP and IL-6 synthesis has been extensively reviewed (Kast, 2000; 2005; 2007). The relationship has been documented specifically in glioblastoma cells (Lin *et al.*, 2009). Because serotonin stimulates the Gs-coupled 5-HT_7 receptor, stimulation of IL-6 by 5-HT_7 agonists was to be expected (Kast, 2007). There are many paths to stimulate adenylate cyclase. Perhaps all of them must be blocked for effective control of IL-6.

Earlier efforts to find paths to lower IL-6 in glioblastoma focused on reducing the component of increased IL-6 in glioblastoma contributed by histaminergic agonism at H_1 receptors (Kast and Altschuler, 2006; Kast, 2007) using potent H_1 receptor blockers (technically they are inverse agonists) currently in wide clinical use – doxopin, mirtazapine or olanzapine (Kast and Altschuler, 2006; Kast, 2007).

Conclusion

That targeting of specific growth factors utilized by a specific cancer in a specific patient will improve outcomes is a current line of thinking (Kast and Altschuler, 2006; Kudo *et al.*, 2009) to which this paper contributes.

We do not know the dosing that will shut down glioblastoma 5-HT7 signalling enough to be of clinical use. Patients with psychosis treated with risperidone at the lower end of its dosing range, 3.5 mg per day, showed 50% to 70% dopamine receptor(2) occupancy and close to 100% 5-HT2A occupancy (Reimold *et al.*, 2007). Although inhibition of 5-HT_7 function by paliperidone, pimozide or risperidone is unlikely to have profound growth retarding or prognosis improving effects given the large number and redundant intersecting nature of growth promoting systems active in glioblastoma, the benign and reversible nature of expected side effects warrant a clinical trial if rodent study confirms activity in growth slowing by 5-HT_7 inhibition.

Conflict of interest

The author has no conflict of interest in any matter related to this work.

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