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DO ATYPICAL ANTIPSYCHOTICS PROMOTE NEUROGENESIS AS A CLASS EFFECT?

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SUMMARY

It has been reported that some atypical antipsychotics promote neurogenesis in the hippocampus and possibly in the frontal cortex. Atypical antipsychotics are a heterogeneous group of drugs. Hence the question arises as to whether neurogenesis is a class effect which relates to them all. We here present a literature search which we have carried out to establish this.

Key words: *neurogenesis – Risperidone – Paloperidol - Olanzapine – Quetiapine – Clozapine – Ziprazidone – Amisulpride - Aripiprazole*

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INTRODUCTION

Neurogenesis has been demonstrated in the Hippocampus and in parts of the frontal cortex first with SSRIs and then with most antidepressants. It has been reported that some atypical antipsychotics promote neurogenesis in the hippocampus and possibly in the frontal cortex. Atypical antipsychotics are a heterogeneous group of drugs. Hence the question arises as to whether neurogenesis is a class effect which relates to them all. We here present a literature search which we have carried out to establish whether this is the case.

METHOD

We carried out the search using Google Scholar and Pubmed. We searched for articles on the different atypical antipsychotics which described either neurogenesis or intracellular markers which suggested neurogenesis may take place.

RESULTS

Risperidone has been shown to have a weak potential for injury in cells, which is sharp contrast to the potential of haloperidol (Ukai 2004). Like other members of the atypical class, risperidone has neurogenic effects (Wakade 2002). Multiple studies have provided further clues as to the molecular effects of atypical drugs, using risperidone as the test drug. It seems that risperidone increases levels of BDNF, c-fos and STAT-3 expression (Tan 2007) – all of which are neurotrophic factors. In addition, risperidone ameliorates the effects of rotenone induced toxicity (Tan 2007), inhibits caspase activation (Gasso 2012) and blocks glutamate induced toxicity (Abekawa 2011). However, since every atypical has a different receptor profile, we cannot extrapolate these effects to other members of the atypical class.

Paliperidone is a metabolite of risperidone, now produced and marketed as an antipsychotic in its own right. Bromodeoxyuridine was injected to label dividing cells and positive cells were quantified in the Olfactory Endothelium, cortical SVZ, and dentate gyrus. of the hippocampus (Nasrallah 2010). Paliperidone and risperidone treatment caused increased numbers compared with controls of Bromodeoxyuridine positive cells in the Olfactory Endothelium and the posterior SubVentricular Zone while paliperidone or risperidone treatment did not increase Bromodeoxyuridine positive cells in the Dentate Girus (Nasrallah 2010). Hanson (2011) has shown that paliperidone increased BDNF mRNA expression in the dentate gyrus 14 days after administration (Hanson 2011). However Paliperidone did not affect neuronal proliferation, either alone or when combined with lithium (Hanson 2011). There was an interaction between lithium and paliperidone in how they affected survival of cells which were to become neurons (Hanson 2011).

Neurogenesis can also be demonstrated also with olanzapine. Olanzapine, but not Haloperidol, has been demonstrated to promote Neurogenesis in Rats (Wang 2004, Csernansky 2006). Kodama in 2004, showed that olanzapine increased the number of newborn cells in the dentate gyrus of the hippocampus to the same extent that fluoxetine did (Kodama 2004). Both Olanzapine and fluoxetine increased the number of proliferating cells in the prelimbic cortex, but not in the subventricular zone or primary motor cortex, while there was a trend for an increase in the striatum (Kodama 2004). It was found that approximately 20% of the newborn cells in the prelimbic cortex differentiated into endothelial cells but not neurons, in contrast

to the dentate gyrus, where most newborn cells differentiated into neurons (Kodama 2004). Thus antidepressant or atypical antipsychotic medications can increase the proliferation of glia in limbic brain structures, an effect that could reverse the loss of glia that has been observed in depressed patients (Kodama 2004).

The effect of quetiapine on neurogenesis has also been studied. Xu has shown that chronic administration of quetiapine attenuates the decrease in levels of brain-derived neurotrophic factor (BDNF) in the hippocampi of rats subjected to chronic-restraint stress (Xu 2002). Luo has also shown that post-stress administration of quetiapine reversed the stress-induced suppression of hippocampal neurogenesis (Luo 2005). It was suggested that this may help us understand the therapeutic effects of quetiapine on cognitive deficits in patients with schizophrenia and depression, in which the structure and functions of the hippocampus are implicated (Luo 2005). However it has also been shown that, in cerebral ischaemia, quetiapine also regulates neurogenesis (Bi 2009) by down-regulating NF-kappaB p65/p50 expression (Bi 2009). This down-regulation actually acts to inhibit neurogenesis, thus regulating it (Bi 2009). Furthermore, Xu has shown (Xu 2006) that Quetiapine and Venlafaxine are synergistic in promoting BDNF expression and neurogenesis in the rat hippocampus(Xu 2006). This was demonstrated in rats who were subjected to chronic restraint stress (Xu 2006). Chronic restraint stress decreased hippocampal cell proliferation and BDNF expression (Xu 2006). However chronic administration of quetiapine or venlafaxine prevented these decreases in hippocampal cell proliferation and BDNF expression caused by chronic restraint stress (Xu 2006). A combination of low doses of quetiapine and venlafaxine increased hippocampal cell proliferation and prevented BDNF decrease in the stressed rats, while these low doses were insufficient to cause such an increase (Xu 2006). Higher doses of quetiapine or venlafaxine demonstrated effects comparable to those produced by their combination (Xu 2006). These laboratory findings have underpinned the use of quetiapine as an antidepressant and the use of quetiapine in combination with antidepressants in the treatment of resistant depression (Xu 2006). Such combinations have recently been incorporated into the NICE guidelines for the treatment of Resistant Depression.

There seems to be more difficulty in demonstrating a positive effect on Neurogenisis by Clozapine. Clozapine pre-treatment and post-treatment has been shown to reverse haloperidol toxicity (Parikh 2004), and increase NGF levels in medication naïve schizophrenia patients back to almost non-pathological levels. Halim (2004) demonstrated that a low dose of clozapine increased the number of BrdU-positive cells in the dentate gyrus (DG) by two-fold, which suggested that clozapine increased cell division (Halim 2004). However Neither clozapine nor haloperidol had any effect on cell proliferation in the dentate gyrus (Halim 2004). Nor did either drug have an effect on the number of newly generated neurons surviving in the dentate gyrus 3 weeks later (Halim 2004). Thus clozapine may influence the number of cells which divide, but neither clozapine nor haloperidol appeared to promote the survival of the newly generated neurons at 3 weeks (Halim 2004). Schmitt (2004) investigated the influence of acute and chronic haloperidol and clozapine treatment on the total number of newly dividing cells and hippocampal volume using an animal model with doses equivalent to the therapeutic range in humans (Schmitt 2004). Neither drug altered the total number of newly dividing cells in the dentate gyrus (Schmitt 2004). However, chronic haloperidol treatment increased total hippocampal volume suggesting that haloperidol alters neuroplastic processes or glial morphology rather than cell proliferation (Schmitt 2004). However, a more recent study (Maeda 2007) showed that, in the dentate gyrus of mice, clozapine, but not haloperidol, prevents a decrease in neurogenesis in mice repeatedly treated with phencyclidine although repeated antipsychotic treatment by themselves (that is, apart from phencyclidine treatment) had no effect on neurogenesis (Maeda 2007). Furthermore, co-administration of D-serine and glycine, but not L-serine, inhibited the PCP-induced decrease in the number of deviding cells (Maeda 2007). These results suggest that chronic dysfunction of NMDA receptors causes a decrease in neurogenesis in the dentate gyrus (Maeda 2007). This is of interest, since it links NMDA receptor dysfunction with possible treatments for schizophrenia.

Regarding Amisulpride, Abbas (2009) demonstrated that Amisulpride is a potent competitive antagonist at 5-HT_{7a} receptors and that interactions with no other molecular target investigated here could explain its antidepressant actions in vivo (Abbas 2009). This was a new finding because the selective D_2/D_3 receptor antagonist properties of amisulpride, has long been assumed to cause its antidepressant and antipsychotic properties (Abbas 2009).The authors linked this finding in their paper with a possible effect of amisulpride on Neurogenesis, although they did not attempt to demonstrate neurogenesis per se in their paper (Abbas 2009). We found no other references to neurogenesis and amisulpride in the literature.

We have found no articles regarding either Aripiprazole or Ziprazidone promoting neurogenesis. However in one study,aripiprazolewas associated with increased BDNF promoter activity,and increased the levels of GSK-3β phosphorylation and Bcl-2 expression (Park 2009). Thus at least aripiprazole, unlike haloperidol, appeared to offer neuroprotective effects on human neuronal cells (Park 2009).

Hence it appears that neurogenesis is a class effect common to most atypical antipychotics (Wakade 2002), particularly those which promote antagonism of 5-HT_{7a} receptors. It is interesting, however that the least evidence for neurogenesis as an important mode of action among the atypical antipsychotics which we have

examined is for clozapine, which is used for resistant schizophrenia. This suggests other modes of action for clozapine. Duncan (2008) has identified Thirteen genes which showed verified regulation by three drugs which were studied- haloperidol, clozapine and olanzapine - three genes were significantly upregulated and ten genes significantly downregulated by treatment (Duncan 2008). These genes encode proteins that function in various biological processes including neurogenesis, cell adhesion, and four genes are involved in voltage-gated ion channels (Duncan 2008). These results show that transcriptional regulation of ion channels, crucial for neurotransmission, as well as neurogenesis and cell-adhesion, may play a role in mediating antipsychotic drug effects (Duncan 2008). This provides different possible modes of action for different medications, and so may explain why different anti-psychotics may have different effects on patients, since these modes of action may be have different relative importance in each drug.

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