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Review

Improving cognition in schizophrenia with antipsychotics that elicit neurogenesis through 5-HT_{1A} receptor activation

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ABSTRACT

Atypical antipsychotics fail to substantially improve cognitive impairment associated with schizophrenia (CIAS) and one strategy to improve it is to stimulate adult neurogenesis in hippocampus, because this structure is part of an altered circuitry that underlies aspects of CIAS. Deficits in hippocampal adult neurogenesis may disrupt cognitive processes that are dependent on newborn neurons, such as pattern separation (the formation of distinct representations of similar inputs). Mechanisms by which hippocampal adult neurogenesis can be increased are therefore of therapeutic interest and a promising molecular target is the activation of serotonin 5-HT_{1A} receptors because agonists at this site increase adult neuronal proliferation in the dentate gyrus. We hypothesize that use of antipsychotics possessing 5-HT_{1A} receptor agonist properties may protect against or attenuate CIAS by a dual mechanism: a favorable influence on adult neurogenesis that develops upon sustained drug treatment, and an increase in dopamine levels in the prefrontal cortex that starts upon acute treatment. This hypothesis is consistent with the beneficial properties of 5-HT_{1A} activation reported from pilot clinical studies using 5-HT_{1A} agonists as adjunct to antipsychotic treatments. Recent antipsychotics, including clozapine and aripiprazole, exhibit different levels of 5-HT_{1A} receptor partial agonism and may, therefore, differentially elicit hippocampal adult neurogenesis and increases in prefrontal cortex dopamine. We suggest that comparative studies should elucidate correlations between effects of antipsychotics on adult neurogenesis and prefrontal cortex dopamine with effects on performance in translational cognitive tasks known to involve new born neurons, such as tasks involving pattern separation, and working memory tasks sensitive to prefrontal cortex dopamine levels.

1. Introduction

Schizophrenia and psychotic disorders constitute a serious mental health problem and a substantial burden on health care (Rossler, Salize, van Os, & Riecher-Rossler, 2005). Although a variety of pharmacological mechanisms have been proposed to underlie antipsychotic efficacy, dopamine D_2 receptor antagonism remains the cornerstone of the activity of current antipsychotic drugs. Indeed, the fundamental concept underlying antipsychotic activity is the dopamine hypothesis (Carlsson, 1988) characterized by subcortical hyper-dopaminergia with prefrontal hypo-dopaminergia (Davis, Kahn, Ko, & Davidson, 1991). Thus, the "first generation" antipsychotic, haloperidol, controls positive symptoms of schizophrenia by opposing the excessive stimulation of D_2 receptors resulting from hyperactivity of mesolimbic dopaminergic projections. However, it fails to alleviate the hypoactivity of mesocortical dopaminergic neurons (*i.e.*, "hypofrontality"), thought to underlie negative symptoms such as social withdrawal and flattened affect, and cognitive deficits including working memory impairment and loss of cognitive flexibility (Meltzer & Sumiyoshi, 2008). Further, selective dopamine D_2 receptor antagonists also block nigrostriatal dopaminergic activity, leading to extrapyramidal symptoms, and pituitary D_2 receptors that control prolactin release, leading to hyperprolactinemia (Goff & Shader, 2003). To overcome these limitations, a variety of "atypical" or "second generation" antipsychotics have been developed that act at other receptors as well as antagonizing D_2 receptors. The "gold standard" among these antipsychotics is clozapine, which is considered to possess superior therapeutic efficacy whilst inducing negligible extrapyramidal symptoms. The molecular targets of clozapine's activity have been

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extensively investigated, with a particular focus on blockade of serotonin 5-HT_{2A} receptors and of dopamine D_3 and D_4 receptors, among others. Whilst selective ligands at these receptors have not shown antipsychotic activity in clinical trials, combinations of these pharmacological activities diminish extrapyramidal symptoms liability and improve negative and cognitive symptoms. Indeed 5-HT_{2A} receptor antagonism favors cortical dopaminergic neurotransmission when associated with D_2 receptor antagonism. Increasing cortical dopamine release is expected to alleviate hypofrontality in schizophrenic patients (Ichikawa & Meltzer, 1999; Lahti et al., 2004) and a variety of "atypical" antipsychotics that combine 5-HT_{2A} receptor antagonism with D_2 receptor antagonism have therefore been developed (e.g., risperidone, olanzapine and ziprasidone) (Richtand et al., 2008). Nevertheless, the ability of these drugs to control negative symptoms and cognitive deficits remains, at best, limited and serious problems of metabolic dysfunction are elicited by olanzapine and clozapine, likely via antagonism of histamine H_1 and 5-HT_{2C} receptors. Further, antagonism of muscarinic M_1 receptors can impair cognitive function.

Taken together, these considerations indicate that, notwithstanding the progress made in the discovery and development of second generation antipsychotics, these have only shown modest advances, compared with first generation antipsychotics (Kane & Correll, 2010). This is perhaps not surprising, as drug discovery efforts typically aim for incremental progress; often selecting existing treatments as a starting point and trying to improve side effect profile. Such a strategy may, however, not take into account potentially game-changing new insights into the pathogenesis of schizophrenia based on genetics, molecular biology, and imaging studies. Recently, a version of the dopamine hypothesis that incorporates these novel insights has been formulated (Howes & Kapur, 2009) and may assist in the development of novel drug discovery strategies.

2. Restoring activity in hippocampal circuits

Despite the efforts described above, few drug treatment strategies have been proposed that address the issue of disease modification, as opposed to symptom management. Indeed, schizophrenia is a disease of dysfunctional circuits and the rationale for novel treatments with disease-modifying potential should aim to repair these circuits. As the severity of deficits in cognitive function in schizophrenia patients is thought to be a key determinant of functional outcome (Goldberg & Green, 2002), identification of the circuits underlying those cognitive processes is therefore of interest. In this context, a large body of data suggests that hippocampal function is involved in the pathophysiology of schizophrenia and that altered wiring in the hippocampus and its extrinsic connections, especially with the prefrontal cortex, underlies neuropsychological impairments. Indeed, several hippocampal abnormalities have been reported. First, a volumetric reduction has been found more often for the hippocampus than for any other brain area affected in schizophrenia. Second, basal perfusion is elevated and partially restored by antipsychotics. Third, using functional MRI BOLD activation methods, alterations in functional activation in conjunctive memory tasks were found (for reviews, see Harrison, 2004; Tamminga, Stan, & Wagner, 2010).

The cellular and molecular mechanisms for hippocampal pathology in schizophrenia are still a matter of debate but human tissue studies point to regional GABAergic and glutamatergic dysfunction (Konradi & Heckers, 2001). In addition, there is increasing awareness of the importance of the generation of functional neurons throughout the entire lifespan, particularly in the subgranular zone (SGZ) of the dentate gyrus (DG), a process that has been termed adult hippocampal neurogenesis. Emerging evidence suggests that deficits in adult neurogenesis may contribute to the decrease in hippocampal volume in schizophrenia. For example, hippocampal neural stem cell proliferation is reduced (Reif, Schmitt, Fritzen, & Lesch, 2007; Reif et al., 2006). These changes in adult neurogenesis may contribute to cognitive impairment associated with schizophrenia (CIAS) in hippocampal-dependent tasks. Effects of antipsychotic drugs on adult neurogenesis in SGZ of the DG are inconsistent (reviewed in Balu & Lucki, 2009; Newton & Duman, 2007; Reif et al., 2007) and, accordingly, only small improvements are observed in cognition, possibly even as a secondary consequence of a reduction in psychotic symptoms (CATIE trial; Keefe et al., 2007). Therefore, the unmet medical need for treating CIAS remains high.

3. Role of adult-newborn neurons in hippocampal functioning: pattern separation

The hippocampus and adjacent cortical areas that are anatomically related, such as the entorhinal cortex, form the medial temporal lobe that has a key role in the control of declarative memory (Zola and Squire et al., 1993). This type of long-term memory can be literally defined as information that can be declared or put in words. It concerns knowledge about facts (semantic memory) and events (episodic memory). Although the precise function of the hippocampus in declarative memory is under discussion, the current knowledge about the trisynaptic pathway in the medial temporal lobe (Tamminga et al., 2010) (see Fig. 1) has informed hypotheses about the role of adult-newborn neurons in the DG. In this view the hippocampus is a gateway for memory and prepares contents for long-term storage in cortical areas (Hasselmo & Eichenbaum, 2005). Adult neurogenesis occurs on the bottleneck of the trisynaptic circuit as pathways from the entorhinal cortex and other areas project to the DG; the output from the DG next reaches neurons in the CA3. It is thought that strategically-introduced single new neurons with unique properties such as increased plasticity (Schmidt-Hieber, Jonas, & Bischofberger, 2004) can increase the complexity that a network can process at a later time (Deng, Aimone, & Gage, 2010; Kempermann, 2002). Computational models (reviewed by (Aimone and Wiskott, 2008)) have helped to further develop the concept that adult neurogenesis endows a network with the ability to adapt to future changes in input. This has also been described as "metaplasticity": a change in the brain that facilitates further changes in the brain (Lledo, Alonso, & Grubb, 2006).

The DG is considered to possess a major role contributing to declarative memory by functioning as a pattern separator, that is, forming distinct representations of similar inputs by differentially encoding small or weak changes from these inputs (Treves, Tashiro, Witter, & Moser, 2008). This is achieved through the dispersion of cortical inputs onto DG granule cells and subsequently CA3 pyramidal cells. Impaired pattern separation in schizophrenia may lead to increased illusory pattern completion and a reduced discrimination between present and past experiences in memory. This would lead to psychotic associations and result in memories with psychotic content (Tamminga et al., 2010). Deficits in declarative memory have been well documented for schizophrenia (Carter & Barch, 2007) and although pattern separation involving the DG/CA3 area) has been demonstrated in humans (Bakker, Kirwan, Miller, & Stark, 2008), the hypothesis that pattern separation is impaired in schizophrenia remains to be tested. Nevertheless, several animal studies support a link between adult neurogenesis and pattern separation (Clelland et al., 2009; Sahay et al., 2011). In adult C57Bl/6 mice with ablated hippocampal neurogenesis, spatial discrimination was impaired in two tasks when stimuli were presented with little spatial separation. In a delayed nonmatching to place eight-arm radial maze task, adult neurogenesis-deficient mice were impaired in their differentiation between locations that