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Research report

Chronic atypical antipsychotics, but not haloperidol, increase neurogenesis in the hippocampus of adult mouse

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ABSTRACT

It is suggested that altered neuroplasticity contributes to the pathophysiology of schizophrenia and antipsychotics may exhibit some of their therapeutic efficacies by improving neurogenesis and/or proliferation of neural progenitors. The aim of this study is to investigate whether chronic antipsychotics treatment affect neurogenesis in adult mouse hippocampus. Animals were administered olanzapine, quetiapine, clozapine, risperidone, aripiprazole, or haloperidol via the osmotic minipump for 21 days and then injected with 5-bromo-2′-deoxyuridine (BrdU) to label mitotic cells. BrdU-positive cells in the hippocampus were quantified by stereology. Aripiprazole, quetiapine, clozapine, and olanzapine significantly increased density of BrdU-positive cells in the hippocampus. Interestingly, other antipsychotic drugs had tendency to increasing BrdU-positive cells, whereas haloperidol had propensity to decrease with a marginal significance. These results suggest that differences of neurogenesis among these drugs may, at least in part, account for their pharmacological profiles.

1. Introduction

Neurogenesis appears to occur throughout the life in the subventricular zone (SVZ) of the lateral ventricle and the subgranule zone (SGZ) of the hippocampus in rodents (Altman and Das, 1965; Kaplan and Hinds, 1977; Markakis and Gage, 1999), non-human primates (Gould et al., 1999; Kornack and Rakic, 1999), and humans (Eriksson et al., 1998). In the SVZ of adult newborn neurons migrate anteriorly into the olfactory bulb (OB), where they mature into local interneurons (Alvarez-Buylla and Garcia-Verdugo, 2002). In the meanwhile, in the hippocampus, neurogenesis in the adult dentate gyrus (DG) originates from a precursor population that resides in the SGZ, a thin band of tissue between the granule cell layer (GCL) and the hilus (Ehninger and Kempermann, 2008). The proliferating cells in the SGZ give rise to mature neurons that migrate into the GCL (Hastings and Gould, 1999) and these new neurons differentiate and appear to have morphological and physiological characteristics that are similar to adult granule cells (van Praag et al., 2002; Malberg and Duman, 2003).

The integration of adult-born neurons into the circuitry of the adult hippocampus has been implicated in physiological brain function such as spatial pattern separation (McHugh et al., 2007; Clelland et al., 2009; Sahay et al., 2011), memory reconsolidation (Kitamura et al., 2009), and stress responses (Snyder et al., 2011). Moreover, alteration of this process has been associated with a number of neuropsychiatric diseases including depression (Gould et al., 1997; Malberg et al., 2000), drug addiction (Nixon and Crews, 2002; Noonan et al., 2008), epilepsy (Parent et al., 2006), and schizophrenia (Keilhoff et al., 2004; Flagstad et al., 2005). Recent studies aimed at understanding the role of neurogenesis in such illnesses have focused more on hippocampal neurogenesis, partially owing to the low numbers of neurons born in the human OB under physiological conditions (Kempermann, 2012). These facts raised new questions on what neurogenesis in this area really means in both pathophysiology of mental diseases and their therapeutic process.

Although the principal brain target that conventional antipsychotic drugs act on is the dopamine D2 receptor, and many typical

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antipsychotics induce extrapyramidal symptoms (EPS) or hyperprolactinemia by acting on it, atypical antipsychotics given in dosages within the clinically effective range do not bring about these adverse clinical effects. To understand how atypical antipsychotics work, it is important to examine their mechanism of action (Seeman, 2002). In fact, the effects of antipsychotics on proliferation and neurogenesis have been investigated in the neurogenetic region of adult animal brain and these studies are closely reviewed elsewhere (Toro and Deakin, 2007). Dawirs et al. found that acute treatment of haloperidol stimulated proliferation of 5-bromo-2′-deoxyuridine (BrdU)-positive cells in the gerbil hippocampus (Dawirs et al., 1998). However, results of subsequent studies in rats differ from the previous one. Wakade et al. reported that repeated treatment of haloperidol for 21 days had no effect on the cell proliferation either in the DG or the SVZ (Wakade et al., 2002). Likewise, Halim et al. found that there was no change in number of BrdU-positive cells in the DG after acute or chronic haloperidol treatment (Halim et al., 2004). Moreover, it was shown by Wang et al. that chronic haloperidol treatment had no changes in proliferation in the medial prefrontal cortex (PFC), striatum (STR), DG, and nucleus accumbens (NAc) (Wang et al., 2004). These results suggest that neurogenesis may play little role in the therapeutic efficacy of haloperidol.

With regard to atypical antipsychotics, results have been more complicated; experimental methods such as types, dosage or periods of drugs used lead to completely different results. It is reported by Wang et al. that olanzapine significantly increased both total number and density of BrdU-labeled cells in the PFC and dorsal striatum (Wang et al., 2004). Similarly, Kodama et al. found that chronic administration of olanzapine increased the number of newborn cells in the DG of hippocampus (Kodama et al., 2004). On the other hand, acute and chronic treatment of clozapine had no effects in another study (Halim et al., 2004). Additionally, Wakade et al. found that chronic risperidone and olanzapine administration induced a significant increase in BrdU-positive cells in SVZ, however, this effect was not seen in the hippocampus (Wakade et al., 2002).

As described above, it remains inconsistent whether antipsychotics, especially atypical antipsychotics, may enhance neurogenesis and proliferation in contrast to antidepressant drugs. Further work is required to resolve these discrepancies because they may be due to diversity not only in the types of antipsychotics used in studies but in their dosages, application regimens, or animal species.

The aim of this study is to investigate effects of antipsychotics on the neurogenesis in the hippocampus. To uncover the effects exhaustively, we examined six of the most commonly used antipsychotics. We reported here that atypical antipsychotics, but not haloperidol, enhance neurogenesis in the mouse hippocampus, which may reflect beneficial properties of these drugs.

2. Result

2.1. BrdU immunohistochemistry

BrdU immunohistochemistry revealed uniformly-stained nuclei which were predominantly distributed in the SGZ throughout the hippocampal structure in all animals examined as we reported previously (Yutsudo et al., 2013), thus, demonstrating that both BrdU administration and the antibodies used in this study were adequate to label newborn cells in this area (Fig. 1).

2.2. Chronic atypical antipsychotics administration increase the number of BrdU-positive cells

We then counted the number of BrdU-positive cells in SGZ using unbiased stereology. We found that chronic atypical antipsychotics administration increased density of BrdU-positive cells in the hippocampus by 30–70% (vehicle, 10182.6 ± 1132.3 cells/mm^3; aripiprazole, 17,606 ± 1132.3 cells/mm^3; clozapine, 16265.4 ± 1200.9 cells/mm^3; olanzapine, 14400.8 ± 1074.2 cells/mm^3; quetiapine, 16804.8 ± 1200.9 cells/mm^3; risperidone, 13036.9 ± 1024.2 cells/mm^3; mean ± SEM) (Fig. 2). Statistical analysis revealed that aripiprazole, clozapine, olanzapine, and quetiapine administration significantly increased BrdU-positive cells in the hippocampus ($F_{6,58} = 10.5$; $p < 0.0001$).

Whereas, chronic administration of haloperidol showed a 23% reduction of BrdU-positive cells compared to the vehicle group (7871.8 ± 1074.2 cells/mm^3; mean ± SEM; $p < 0.05$). This indicates that an increase in density of BrdU-positive cells may be specific to atypical antipsychotics.

3. Discussion

This is the first study that examines the effect of antipsychotics on the hippocampal neurogenesis exhaustively. We revealed in this study that chronic atypical antipsychotics administration increased the density of BrdU-positive cells in SGZ by 30–70%, and this effect was not observed in haloperidol treatment. The fact that upregulation of neurogenesis was only observed in atypical antipsychotics may reflect these drugs share pharmacologically similar mechanism of action.

Previous studies have demonstrated that haloperidol had no effects on hippocampal neurogenesis (Malberg et al., 2000; Wakade et al., 2002; Wang et al., 2004; Halim et al., 2004), which is in line with our result. This result seems valid because haloperidol is a potent dopamine D2 antagonist and basically exerts its pharmacological action by blocking D2 receptors. This result is also replicated by a recent study that another D2 receptor antagonist sulpiride had no effect on the cell number of adult rat DG-derived neural precursor cells (Takamura et al. 2014). Keilhoff et al. exceptionally reported that very small amount of haloperidol increased BrdU-positive cells in DG and normalized vitamin D-deficient-induced reduction of cell proliferation (Keilhoff et al., 2010). The difference between these results may be interpreted as follows; administration of haloperidol does not affect or would rather decrease neurogenesis or cell proliferation at a normal therapeutic dose, whereas, subclinical dose of this drug may act in a quite different way. Although the effect of different doses of haloperidol on neurogenesis has not been investigated yet, this notion has been supported by the studies of ketamine, a glutamate NMDA (N-methyl-D-aspartate) receptor antagonist. At a normal dose, ketamine interferes with cell proliferation and differentiation of neural stem cells (Huang et al., 2015), on the contrary, subanesthetic doses of ketamine applied subchronically enhance neurogenesis in SGZ (Keilhoff et al., 2004). In any case, it is unlikely that haloperidol produces its therapeutic actions through stimulation of neurogenesis under the normal dose for treatment.

As mentioned above, it is controversial whether atypical antipsychotics increase neurogenesis in the hippocampus, thus we should closely discuss our findings. Xu et al. demonstrated that chronic administration of 5 or 10 mg/kg of quetiapine increase number of BrdU-labeled cells in DG at a dose-dependent manner (Xu et al., 2006). It is also demonstrated that 2 mg/kg of olanzapine, but not 0.5 mg/kg, administration increased the number of neurons both in the DG and prelimbic cortex as the same extend as fluoxetine, a selective serotonin reuptake inhibitor (SSRI) (Kodama et al., 2004). Interestingly, they also demonstrated that most new born cells differentiated into neurons in the DG, in contrast to the prelimbic cortex, where approximately 20% of new born cells differentiated into endothelial cells but not neurons, and concluded that their results represent antidepressant effect