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# Glucocorticoids and Lithium in Adult Hippocampal Neurogenesis

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**Running Title:** GCs and Li in adult hippocampal neurogenesis

## Summary

Adult hippocampal neurogenesis is decreased in rodent models for stress-related disorders partly through an elevated level of glucocorticoids (GCs). On the other hand, lithium (Li), a mood stabilizer and an inhibitor of GSK-3 $\beta$ , increases adult hippocampal neurogenesis. However, it remains unclear whether GCs-induced its decrease can be recovered by Li or not. Recently we established the culture system of adult rat dentate gyrus-derived neural precursor cell (ADP) and examined GCs and Li actions on ADP proliferation. GCs decreased ADP proliferation and Li recovered it. Both cyclin D1 expression and nuclear  $\beta$ -catenin are also reciprocally regulated by GCs and Li. In addition, GCs activated GSK-3 $\beta$ . Therefore, GSK-3 $\beta$ / $\beta$ -catenin pathway may be important in the reciprocal actions of GCs and Li on ADP proliferation. In this manuscript we review the past literature and our study and summarize what is currently known about the effects of GCs and Li on adult hippocampal neurogenesis.

**Key Words:** dexamethasone, dentate gyrus, neural precursor cell, GSK-3 $\beta$ ,

$\beta$ -catenin, cyclin D1, mood disorder

## 1. Introduction

Mood disorders, including major depression and bipolar disorder, are severe, chronic illness which affects 8-12% or 1-6% of general population, respectively (Lopez et al., 2006; Judd and Akiskal, 2003). Although now we have a broad range of drugs such as mood stabilizers like lithium (Li) or antidepressants like fluoxetine, the effectiveness of such drugs on mood disorders is still unsatisfactory. Thus, we can regard them as the most prevalent and costly brain disorders and it is urgent issue to understand their pathophysiology and develop more effective treatments for them.

Mood disorders are often triggered by considerable psychosocial stress. It has been well established that elevated levels of glucocorticoids (GCs) constitute one of causal events in stress-related disorders (de Kloet et al., 2005). Receptors for GCs such as glucocorticoid and mineralcorticoid

receptors (GR and MR) are mainly expressed in the hippocampus in adult brain (Sapolsky et al., 2000). Neurogenesis occurs in adult human hippocampus (Eriksson et al., 1998) and is highly regulated by a variety of environmental, endocrinal and pharmacological stimuli (Warner-Schmidt and Duman, 2006; Sahay and Hen, 2007). Therefore, these facts make us focus on the involvement of adult hippocampal neurogenesis in the pathophysiology and/or drug therapy of mood disorders.

This manuscript begins with an introduction of adult hippocampal neurogenesis and then refers to important findings about the effects of GCs and lithium (Li) on adult hippocampal neurogenesis. Finally, the reciprocal action mechanism of GCs and Li for adult hippocampal neurogenesis will be discussed on the basis of our study.

## **2. Differentiatinal steps of adult hippocampal neurogenesis**

Neurogenesis has been identified in adult brain of various species, including mouse, rat, guinea pig, primate and human (Altman and Das,

1967; Cameron *et al.*, 1993; Kempermann *et al.*, 1997; Eriksson *et al.*, 1998; Gould *et al.*, 1999). It mainly occurs in two discrete brain regions such as the subventricular zone (SVZ) (Alvarez-Buylla and Garcia-Verdugo, 2002) and the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus (Kempermann *et al.*, 2006). In adult human, neurogenesis has been shown only in the DG (Eriksson *et al.*, 1998).

Adult hippocampal neurogenesis to neural lineage can be divided into two phases; Precursor cell phase and Postmitotic maturation phase. On the basis of the expression pattern of marker proteins, four distinct stages (type-1 cells, type-2a cells, type-2b cells and type-3 cells) have been identified in precursor cell phase (Fig.1) (Kempermann *et al.*, 2004; Steiner *et al.*, 2006). It remains unclear when the decision of cell fate is made. However, it must occur on the level of type-2a cells because the marker proteins of immature neuron, including Prox1, NeuroD, doublecortin and PSA-NCAM, is expressed in type-2b cells, but not in type-2a cells. Both type-1 cells and type-2 cells can respond to extrinsic stimuli such as voluntary wheel running or

antidepressants (Nakagawa *et al.*, 2002; Huttmann *et al.*, 2003; Kronenberg *et al.*, 2003; Encinas *et al.*, 2006; Kunze *et al.*, 2006; Segi-Nishida *et al.*, 2008). However, type-2a cells may be the main target of extrinsic stimuli increasing the proliferation of neural precursor cells in adult DG because the burden of cell proliferation lies on type-2a cells in precursor cell phase (Kronenberg *et al.*, 2003).

In postmitotic maturation phase, the dendrite development is initiated (Zhao *et al.*, 2006) and the postmitotic markers such as NeuN are expressed (Brandt *et al.*, 2003). However, the number of NeuN-positive new immature neuron is decreased dramatically within a few days (Brandt *et al.*, 2003). This process has been shown to be apoptotic (Biebl *et al.*, 2000; Kuhn *et al.*, 2005) and regulated by NMDA-type glutamate receptor-mediated input activity (Tashiro *et al.*, 2006). Following to this elimination process, new immature neurons translocate from SGZ into the molecular cell layer and come to rest in the lower third of the granular cell layer. Then, the upper two-thirds of the DG emerge to be occupied predominantly by new immature

neurons derived from neural precursor cells in SGZ (Ahn and Joyner., 2005; Espósito *et al.*, 2005; Laplagne *et al.*, 2006). The number of excitatory synapses grows in following two months and plateaus. Further structural alterations occur for months.

### **3. Stress and glucoorticoids actions on adult hippocampal neurogenesis**

Stress is the most notorious negative regulator of adult hippocampal neurogenesis. Acute stress such as resident-intruder model, predator odor, restraint, or electrical foot shocks, dramatically decreases cell proliferation in adult dentate gyrus (Gould *et al.*, 1997; Tanapat *et al.*, 2001; Pham *et al.*, 2003; Marberg and Duman, 2003). In addition to acute stress, it has been shown that chronic mild stress, which recapitulates the behavioral characteristics of depression rather than acute stress (Willner, 1990), also decreases adult hippocampal neurogenesis (Alonso *et al.*, 2004; Jayatissa *et al.*, 2006; Silva *et al.*, 2008).

Stressful events activate the hypothalamic-pituitary-adrenal (HPA) axis in animals including human. First, the paraventricular nucleus of the hypothalamus secretes corticotrophin-releasing factor (CRF), which stimulates the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary. Next, ACTH stimulates the release of GCs from the adrenal gland and the levels of GCs in blood and cerebrospinal fluid is elevated. Although the elevated levels of them are reversed by the negative-feedback loop in healthy subjects, it does not often work in depressive subjects and the hyper activity of HPA axis and the elevated levels of GCs are continued (de Kloet *et al*, 2005). Therefore, GCs must be one of mediators of stress and may be involved in stress action on adult hippocampal neurogenesis. Actually, psychosocial stress paradigms elevate the levels of them in animal model (Fuchs *et al*, 1998) and a sustained increase in plasma GCs suppresses proliferation of neural precursor cells in the dentate gyrus (Gould *et al.*, 1992; Ambrogini *et al.*, 2002).

Many studies of GCs action on adult hippocampal neurogenesis have

focused attention on cell proliferation and have shown that GCs decrease cell proliferation in adult dentate gyrus (Gould *et al.*, 1997; Cameron and McKay, 1999). Therefore, we also focus attention on GCs action on the proliferation of neural precursor cells in adult DG in this manuscript.

Both of GR and MR are mainly expressed on the nuclear membrane and acts as transcription factors when a ligand binds to them (Sapolsky *et al.*, 2000). It has been shown that GR is expressed in all stages including type-1 cells and type-2a cells and that MR is expressed only in mature cells (Garcia *et al.*, 2004). In addition, dexamethasone (DEX), a specific agonist of GR, decreases cell proliferation in adult hippocampus (Kim J.B. *et al.*, 2004) and mifepristone, a specific antagonist of GR, recovers corticosterone-induced decrease of cell proliferation in adult hippocampus (Mayer *et al.*, 2006). These studies suggest that GR is involved in cell proliferation rather than MR in adult hippocampal neurogenesis.

To investigate the direct effects of various factors and drugs, we recently established the *in vitro* culture system of adult rat dentate gyrus-derived

neural precursor cell (ADP) (Boku *et al.*, 2009). The expression pattern of marker proteins in ADP and its limited proliferation potency indicates that ADP corresponds to type-2a cell. In addition, ADP expresses GR but not MR as in the case with type-2a cell *in vivo*. We examined the direct effects of DEX on ADP and found that DEX decreased ADP proliferation on dose-dependent manner (Boku *et al.*, 2009). Therefore, GCs may directly decrease the proliferation of neural precursor cells.

#### **4. Lithium action on adult hippocampal neurogenesis**

Li is a common mood stabilizer and used for the treatment of bipolar disorder. It is also often used for the augmentation therapy of refractory depression. However, the mechanism underlying the therapeutic effects of Li on mood disorders is poorly understood. It has been well established that Li increases adult hippocampal neurogenesis in rodents (Chen *et al.*, 2000; Son *et al.*, 2003; Kim, J.S. *et al.*, 2004). On the other hand, stress decreases adult hippocampal neurogenesis as described above. We examined the effect of Li

on the proliferation of ADP (Boku *et al.*, 2009). The results showed that only Li had no effect on ADP proliferation. Interestingly, Li could recover DEX-induced decrease of ADP proliferation. Taken together, it is assumed that the therapeutic effects of Li on mood disorders are at least partly mediated by its effects on adult hippocampal neurogenesis.

Two molecules are well known as the targets for Li as their inhibitors: glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) (Klein and Melton, 1996; Stambolic *et al.*, 1996) and inositol monophosphatase (Atack *et al.*, 1995). GSK-3 $\beta$  is a key regulator of  $\beta$ -catenin pathway (also known as canonical Wnt pathway) (Aberle *et al.*, 1997; Orford *et al.*, 1997). Moreover, the activation of  $\beta$ -catenin pathway increases cell proliferation through promoting cyclin D1 expression in tumor-derived cell line (Tetsu and McCormick, 1999; Shtutman *et al.*, 1999). These studies suggest that GSK-3 $\beta$  may be essential for Li action on adult hippocampal neurogenesis. Actually, recent studies have shown that GSK-3 $\beta$  and  $\beta$ -catenin pathway is involved in adult hippocampal neurogenesis both *in vivo* (Lie *et al.*, 2005; Eom and Jope, 2009) and *in vitro*

(Wexler *et al.*, 2008). In addition, we have also shown that DEX decreases nuclear  $\beta$ -catenin and the expression of cyclin D1 in ADP. Conversely, Li recovers them. (Boku *et al.*, 2009). Taken together, Li may increase adult hippocampal neurogenesis through inhibiting GSK-3 $\beta$  and following activation of  $\beta$ -catenin pathway.

Our results described above also suggest that DEX may activate GSK-3 $\beta$ . However, it is not known whether GCs are involved in the regulation of GSK-3 $\beta$  and  $\beta$ -catenin pathway. To elucidate it, we examined the effects of DEX on the phosphorylation of Ser<sup>9</sup> and Tyr<sup>216</sup> of GSK-3 $\beta$  in ADP because the activity of GSK-3 $\beta$  is regulated by two phosphorylated residues; Ser<sup>9</sup> to render it inactive (Cross *et al.*, 1995) and Tyr<sup>216</sup> to render it active (Hughes *et al.*, 1993). DEX had no effect on the phosphorylation of Ser<sup>9</sup> but remarkably increased that of Tyr<sup>216</sup>. On the other hand, Li had no effect on both of them. In addition, DEX had no effect on the expression of GSK-3 $\beta$  (Boku *et al.*, 2009). Therefore, DEX is considered to inhibit  $\beta$ -catenin pathway through activating GSK-3 $\beta$  and Li is considered to recovers

DEX-induced inactivation of  $\beta$ -catenin pathway through inhibiting activated GSK-3 $\beta$  (Fig.2).

## 5. Concluding remarks

GCs are key mediators of stress and Li is commonly used for the treatment of stress-related disorders. It has been well established that adult hippocampal neurogenesis is involved in the therapeutic action of drugs for stress-related disorders. Moreover, many evidences for the involvement of GCs and Li in the regulation of adult hippocampal neurogenesis have been accumulated. Therefore, we can consider that GCs and Li reciprocally regulate adult hippocampal neurogenesis. Our recent study is the first study showed that GCs and Li reciprocally regulated the proliferation of adult DG-derived neural precursor cell. In addition, we found that GSK-3 $\beta$  and  $\beta$ -catenin pathway was involved in it. Our study was performed *in vitro* culture system. Therefore, further *in vivo* experiments are necessary for confirming our hypothesis about the mechanism of the reciprocal effects of

glucocorticoids and Li on adult hippocampal neurogenesis.

In contrast to us, Wexler et al have shown that Li increases the proliferation of neural precursor cells derived from adult entire hippocampus without DEX (Wexler *et al.*, 2008). The discrepancy between our result and Wexler's one might be due to the difference of the source and character of cells as well as culture condition. We have no answer regarding which culture condition and reactivity to Li is closer to those of in vivo neural precursor cells in adult DG. To answer this question is necessary for a further understanding of the direct effects of Li on neural precursor cell in adult DG. Nonetheless, these studies suggest that Li may directly affect the proliferation of neural precursor cell in adult DG.

Our study suggests that the expression of cyclin D1 is decreased by DEX through inactivating  $\beta$ -catenin pathway. However, There is the possibility that GR directly represses the transcription of cyclin D1 because GR is a transcription factor that can promote or repress the transcription of various genes through direct binding to their promoters (Schoneveld *et al.*, 2004).

Our results do not exclude this possibility, and this direct mechanism could regulate ADP proliferation in cooperation with  $\beta$ -catenin pathway.

In this manuscript we have focused attention on the proliferation of neural precursor cell and not referred to neural differentiation and cell survival (anti-apoptosis) of neural precursor cell, both are also essential components of neurogenesis. Several studies have shown that GCs decrease the rate of neural differentiation (Wong and Herbert, 2006) and cell survival (Heine *et al.*, 2004). In addition, Li increases the rate of neural differentiation (Kim, J.S. *et al.*, 2004) or cell survival (Chen *et al.*, 2000) in adult hippocampus. We also have shown that Li promotes both neural differentiation and cell survival in ADP (our unpublished data). Therefore, both GCs and Li can affect not only proliferation but also neural differentiation and cell survival of neural precursor cell in adult hippocampus. To elucidate the functional significance of each component in adult hippocampus is expected to discover the new target for drugs to mood disorders.

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**Figure 1. Differentiation phases in adult hippocampal neurogenesis.**

See text for details. The determination of cell fate is assumed to be made in type-2a cells. In this figure we present only neural lineage. GFAP: glial fibrillary acidic protein, SOX2: sex determining region Y-box2, DCX: doublecortin, CR: calretinin, CB: calbindin.

**Figure 2. Schematic drawing of the proposed mechanism underlying the reciprocal effects of glucocorticoids and Li on ADP proliferation**

DEX activates GSK-3 $\beta$  through increasing Tyr<sup>216</sup> phosphorylation on it and activated GSK-3 $\beta$  phosphorylates  $\beta$ -catenin. Then,  $\beta$ -catenin is degraded and the expression of cyclin D1 is decreased. On the other hand, Li inhibits DEX-activated GSK-3 $\beta$  and decreases the phosphorylation of  $\beta$ -catenin. Then, the nuclear translocation of  $\beta$ -catenin is decreased and the transcription of cyclin D1 gene is increased.

Figure.1

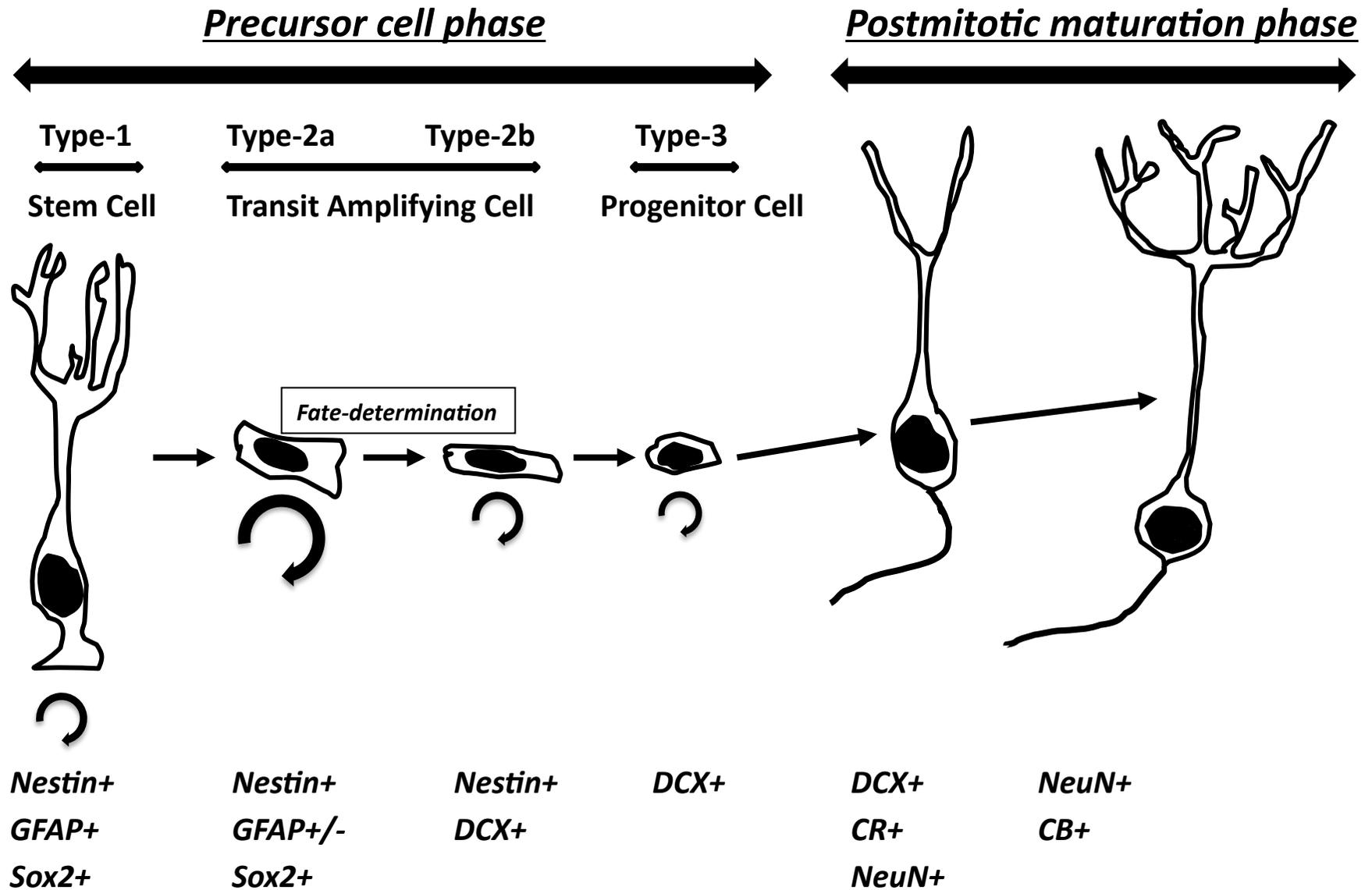


Figure.2

