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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 β , 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 β -catenin are also reciprocally regulated by GCs and Li. In addition, GCs activated GSK-3 β . Therefore, GSK-3 β / β -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 β ,

β -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 β (GSK-3 β) (Klein and Melton, 1996; Stambolic *et al.*, 1996) and inositol monophosphatase (Atack *et al.*, 1995). GSK-3 β is a key regulator of β -catenin pathway (also known as canonical Wnt pathway) (Aberle *et al.*, 1997; Orford *et al.*, 1997). Moreover, the activation of β -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 β may be essential for Li action on adult hippocampal neurogenesis. Actually, recent studies have shown that GSK-3 β and β -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 β -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 β and following activation of β -catenin pathway.

Our results described above also suggest that DEX may activate GSK-3 β . However, it is not known whether GCs are involved in the regulation of GSK-3 β and β -catenin pathway. To elucidate it, we examined the effects of DEX on the phosphorylation of Ser⁹ and Tyr²¹⁶ of GSK-3 β in ADP because the activity of GSK-3 β is regulated by two phosphorylated residues; Ser⁹ to render it inactive (Cross *et al.*, 1995) and Tyr²¹⁶ to render it active (Hughes *et al.*, 1993). DEX had no effect on the phosphorylation of Ser⁹ but remarkably increased that of Tyr²¹⁶. On the other hand, Li had no effect on both of them. In addition, DEX had no effect on the expression of GSK-3 β (Boku *et al.*, 2009). Therefore, DEX is considered to inhibit β -catenin pathway through activating GSK-3 β and Li is considered to recovers

DEX-induced inactivation of β -catenin pathway through inhibiting activated GSK-3 β (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 β and β -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 β -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 β -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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7. References

Aberle, H., Bauer, A., Stappert, J., Kispert, A., Kemler, R. (1997).

Betacatenin is a target for the ubiquitin-proteasome pathway. *EMBO J* 16, 3797-3804.

Ahn, S., and Joyner, A.L. (2005). In vivo analysis of quiescent adult neural stem cells responding to Sonic Hedgehog. *Nature* 437, 894-897.

Ambrogini, P., Orsini, L., Mancini, C., Ferri, P., Bardanti, I., Cuppini, R.

(2002). Persistently high corticosterone levels but not normal circadian fluctuations of the hormone affect cell proliferation in the adult rat dentate gyrus. *Neuroendocrinology* 76, 366-372.

Alonso, R., Griebel, G., Pavone, G., Stemmelin, J., Le Fur, G., Soubrie, P.

(2004). Blockade of CRF(1) or V(1b) receptors reverses stress-induced

suppression of neurogenesis in a mouse model of depression. *Mol Psychiatry* 9, 278-286.

Altman, J., and Das, G.D. (1967). Postnatal neurogenesis in the guinea-pig. *Nature* 214, 1098-1101.

Alvarez-Buylla, A., and Garcia-Verdugo, J.M. (2002). Neurogenesis in the adult subventricular zone. *J Neurosci* 22, 629-634.

Atack, J.R., Broughton, H.B., Pollack, S.J. (1995). Inositol monophosphatase —a putative target for Li⁺ in the treatment of bipolar disorder. *Trends Neurosci* 18, 343-349.

Biebl, M., Cooper, C.M., Winkler, J., Kuhn, H.G. (2000). Analysis of neurogenesis and programmed cell death reveals a self-renewing capacity in the adult rat brain. *Neurosci Lett* 291, 17-20.

Boku, S., Nakagawa, S., Masuda, T., Nishikawa, H., Kato, A., Kitaichi, Y., Inoue, T., Koyama, T. (2009). Glucocorticoids and lithium reciprocally regulate the proliferation of adult dentate gyrus-derived neural precursor cells through GSK-3 β and β -catenin/TCF pathway.

Neuropsychopharmacology 34, 805-815.

Brandt, M.D., Jessberger, S., Steiner, B., Kronenberg, G., Reuter, K., Bick-Sander, A., von der Behrens, W., Kempermann, G. (2003). Transient calretinin expression defines early postmitotic step of neuronal differentiation in adult hippocampal neurogenesis of mice. *Mol Cell Neurosci* 24, 603-613.

Cameron, H.A., and McKay, R.D.G. (1999). Restoring production of hippocampal neurons in old age. *Nat Neurosci* 2, 894-897.

Cameron, H.A., Wooley C.S., McEwen, B.S., Gould, E. (1993). Differentiation of new born neurons and glia in the dentate gyrus of the adult rat. *Neuroscience* 56, 337-344.

Chen, G., Rajkowska, G., Du, F., Seraji-Bozorgzad, N., Manji, H.K. (2000). Enhancement of hippocampal neurogenesis by lithium. *J Neurochem* 75, 1729-1734.

Cross, D.A., Alessi, D.R., Cohen, P., Andjelkovich, M., Hemmings, B.A. (1995). Inhibition of glycogen synthase kinase-3 by insulin mediated by

protein kinase B. *Nature* 378, 785-789.

de Kloet, E.R., Joels, M., Holsboer, F. (2005). Stress and the brain: from adaptation to disease. *Nat Rev Neurosci* 6: 463-475.

Encinas, J.M., Vaahtokari, A., Enikolopov, G. (2006) Fluoxetine targets early progenitor cells in the adult brain. *Proc Natl Acad Sci USA* 103, 8233-8238.

Eom, T.Y., and Jope, R.S. (2009). Blocked inhibitory serine-phosphorylation of glycogen synthase kinase-3alpha/beta impairs in vivo neural precursor cell proliferation. *Biol Psychiatry* 66, 494-502.

Eriksson, P.S., Perfilieva, E., Bjork-Eriksson, T, Alborn, A.M., Nordborg, C., Peterson, D.A., Gage, F.H. (1998). Neurogenesis in the adult hippocampus. *Nat Med* 4, 1313-1317.

Fuchs, E., and Flügge, G. (1998). Stress, glucocorticoids and structural plasticity of the hippocampus. *Neurosci Biobehav Rev* 23, 295-300.

Garcia, A., Steiner, B., Kronenberg, G., Bick-Sander, A., Kempermann, G. (2004). Age-dependent expression of glucocorticoid and mineralcorticoid

receptors on neural precursor cell populations in the adult murine hippocampus. *Aging Cell* 3, 363-371.

Gould, E., Cameron, H.A., Daniels, D.C., Woolley, C.S., McEwen, B.S. (1992). Adrenal hormones suppress cell division in the adult rat dentate gyrus. *J Neurosci* 12, 3642-3650.

Gould, E., McEwen, B.S., Tanapat, P., Galea, L.A.M., Fuchs, E. (1997). Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. *J Neurosci* 17, 2492-2498.

Gould, E., Reeves, A.J., Fallah, M., Tanapat, P., Gross, C.G., Fuchs, E. (1999). Hippocampal neurogenesis in adult Old World primates. *Proc natl Acad Sci USA* 96, 5263-5267.

Heine, V.M., Maslam, S., Zareno, J., Joëls, M., Lucassen, P.J. (2004). Suppressed proliferation and apoptotic changes in the rat dentate gyrus after acute and chronic stress are reversible. *Eur J Neurosci* 19, 131-144.

Hughes, K., Nikolakaki, E., Plyte, S.E., Totty, N.F., Woodgett, J.R. (1993).

Modulation of the glycogen synthase kinase-3 family by tyrosine phosphorylation. *EMBO J* 12, 803-808.

Huttmann, K., Sadgrove, M., Wallraff, A., Hinterkeuser, S., Steinhauser, C., Gray, W.P. (2003). Seizures preferentially stimulate proliferation of radial glia-like astrocytes in the adult dentate gyrus: Functional and immunocytochemical analysis. *Eur J Neurosci* 18, 2769-2778.

Jayatissa, M.N., Bisgaard, C., Tingström, A., Papp, M., Wiborg, O. (2006). Hippocampal cytogenesis correlates to escitalopram-mediated recovery in chronic mild stress rat model of depression. *Neuropsychopharmacology* 31, 2395-2404.

Judd, L.L., and Akiskal, H.S. (2003). The prevalence and disability of bipolar spectrum disorders in the US population: Re-analysis of the ECA database taking into account subthreshold cases. *J Affect Disord* 73, 123-131.

Kempermann, G., Chesler, E.J., Lu, L., Williams, R.W., Gage, F.H. (2006). Natural variation and genetic covariance in the adult hippocampal neurogenesis. *Proc Natl Acad Sci USA* 103, 780-785.

Kempermann, G., Jessberger, S., Steiner, B., Kronenberg, G. (2004).

Milestones of neuronal development in the adult hippocampus. *Trends Neurosci* 27, 447-452.

Kempermann, G., Kuhn, H.G., Gage, F.H. (1997). More hippocampal neurons in the adult mice living in an enriched environment. *Nature* 386, 493-495.

Kim, J.B., Ju, J.Y., Kim, J.H., Kim, T.Y., Yang, B.H., Lee, Y.S., Son H. (2004). Dexamethasone inhibits proliferation of adult hippocampal neurogenesis in vivo and in vitro. *Brain Res* 1027, 1-10.

Kim, J.S., Chang, M.Y., Yu, I.T., Kim, J.H., Lee, S.H., Lee, Y.S., Son, H. (2004). Lithium selectively increases neuronal differentiation of hippocampal neural progenitor cells both in vitro and in vivo. *J Neurochem* 89, 324-336.

Klein, P.S., and Melton, D.A. (1996). A molecular mechanism for the effect of lithium on development. *Proc Natl Acad Sci USA* 93, 8455-8459.

Kronenberg, G., Reuter, K., Steiner, B., Brandt, M.D., Jessberger, S.,

Yamaguchi, M., Kempermann, G. (2003). Subpopulations of proliferating cells of the adult hippocampus respond differently to physiologic neurogenic stimuli. *J Comp Neurol* 467, 455-463.

Kuhn, H.G., Biebl, M., Wilhelm, D., Li, M., Friedlander, R.M., Winkler, J. (2005). Increased generation of granule cell in adult Bcl-2-overexpressing mice: A role for cell death during continued hippocampal neurogenesis. *Eur J Neurosci* 22, 1907-1915.

Kunze, A., Grass, S., Witte, O.W., Yamaguchi, M., Kempermann, G., Redecker, C. (2006). Proliferative response of distinct hippocampal progenitor cell populations after cortical infarcts in the adult brain. *Neurobiol Dis* 21, 324-332.

Laplagne, D.A., Esposito, M.S., Piatti, V.C., Morgenstern, N.A., Zhao, C., van Praag, H., Gage, F.H., Schinder, A.F. (2006). Functional convergence of neurons generated in the developing and adult hippocampus. *Plos Biol* 4, e409.

Lie, D.C., Colamarino, S.A., Song, H.J., Desire, L., Mira, H., Consiglio, A.,

Lein, E.S., Jessberger, S., Lansford, H., Dearie, A.R., Gage, F.H. (2005). Wnt signaling regulates adult hippocampal neurogenesis. *Nature* 437, 1370-1375.

Lopez, A.D., Mathers, C.D., Ezzati, M., Jamison, D.T., Murray, C.J. (2006). Global and regional burden of disease and risk factors, 2001: systemic analysis of population health data. *Lancet* 367, 1747-1757.

Marberg, J.E., and Duman, R.S. (2003). Cell proliferation in the adult hippocampus is decreased by inescapable stress: reversal by fluoxetine treatment. *Neuropsychopharmacology* 28, 1562-1571.

Mayer, J.L., Klumpers, L., Maslam, S., de Kloet, E.R., Joels, M., Lucassen, P.J. (2006). Brief treatment with the glucocorticoid receptor antagonist mifepristone normalizes the corticosterone-induced reduction of adult hippocampal neurogenesis. *J Neuroendocrinol* 18, 629-631.

Nakagawa, S., Kim, J.E., Lee, R., Malberg, J.E., Chen, J., Steffen, C., Zhang, Y.J., Nestler, E.J., Duman, R.S. (2002). Regulation of neurogenesis in adult mouse hippocampus by cAMP and the cAMP response element-binding protein. *J Neurosci* 22, 3673-3682.

Orford, K., Crockett, C., Jensen, J.P., Weissman, A.M., Byers, S.W. (1997).

Serine phosphorylation-regulated ubiquitination and degradation of beta-catenin. *J Biol Chem* 272, 24375-24378.

Pham, K., Nacher, J., Hof, P.R., McEwen, B.S. (2003). Repeated restraint stress suppresses neurogenesis and induces biphasic PSA-NCAM expression in the adult rat dentate gyrus. *Eur J Neurosci* 17, 879-886.

Sahay, A., and Hen, R. (2007). Adult hippocampal neurogenesis in depression. *Nat Neurosci* 10, 1110-1115.

Sapolsky, R.M., Romero, L.M., Munck, A.U. (2000). How do glucocorticoids influence stress response? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev* 21, 55-89.

Schoneveld, O.J.L.M., Gaemers, I., Lamers, W.H. (2004). Mechanisms of glucocorticoid signaling. *Biochim Biophys Acta* 1680, 114–128.

Segi-Nishida, E., Warner-Schmidt, J.L., Duman, R.S. (2008). Electroconvulsive seizure and VEGF increase the proliferation of neural stem-like cells in rat hippocampus. *Proc Natl Acad Sci USA* 105,

11352-11357.

Shtutman, M., Zhurinsky, J., Simcha, I., Albanese, C., D'amico, M., Pestell, R., Ben-Ze'ev, A. (1999). The cyclin D1 gene is a target of the β -catenin/LEF-1 pathway. *Proc Natl Acad Sci USA* 96, 5522-5527.

Silva, R., Mesquita, A.R., Bessa, J., Sousa, J.C., Sotiropoulos, I., Leão, P., Almeida, O.F., Sousa, N. (2008). Lithium blocks stress-induced changes in depressive-like behavior and hippocampal cell fate: the role of glycogen-synthase-kinase-3beta. *Neuroscience* 152, 656-669.

Son H., Yu, I.T., Hwang, S.J., Kim, J.S., Lee, S.H., Lee, Y.S., Kaang, B.K. (2003). Lithium enhances long-term potentiation independently of hippocampal neurogenesis in the rat dentate gyrus. *J Neurochem* 85, 872-881.

Stambolic, V., Ruel, L., Woodgett, J.R. (1996). Lithium inhibits glycogen synthase kinase-3 activity and mimics wingless signaling in intact cells. *Curr Biol* 6: 1644-1668.

Steiner, B., Klempin, F., Wang, L., Kott, M., Kettenmann, H., Kempermann,

G. (2006). Type-2 cells as link between glial and neuronal lineage in adult hippocampal neurogenesis. *Glia* 54, 805-814.

Tanapat, P., Hastings, N.B., Rydel, T.A., Galea, L.A., Gould, E. (2001). Exposure to fox odor inhibits cell proliferation in the hippocampus of adult rats via an adrenal hormone-dependent mechanism. *J Comp Neurol* 437, 496-504.

Tashiro, A., Sandler, V.M., Toni, N., Zhao, C., Gage, F.H. (2006). NMDA-receptor-mediated, cell-specific integration of new neurons in adult dentate gyrus. *Nature* 442, 929-933.

Tetsu, O., and McCormick, F. (1999). β -Catenin regulates expression of cyclin D1 in colon carcinoma cells. *Nature* 398, 422-426.

Warner-Schmidt, J.L., and Duman, R.S. (2006). Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. *Hippocampus* 16, 239-249.

Wexler, E.M., Geschwind, D.H., Palmer, T.D. (2008). Lithium regulates adult hippocampal progenitor development through canonical Wnt pathway

activation. *Mol Psychiatry* 13, 285-292.

Willner, P. (1990). Animal models of depression: an overview. *Pharmacol Ther* 45, 425-455.

Wong, E.Y.H., and Herbert, J. (2006). Raised circulating corticosterone inhibits neuronal differentiation of progenitor cells in the adult hippocampus. *Neuroscience* 137, 83-92.

Zhao, C., Teng, E.M., Summers, R.G., Jr., Ming, G.L., Gage, F.H. (2006). Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. *J Neurosci* 26, 3-11.

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 β through increasing Tyr²¹⁶ phosphorylation on it and activated GSK-3 β phosphorylates β -catenin. Then, β -catenin is degraded and the expression of cyclin D1 is decreased. On the other hand, Li inhibits DEX-activated GSK-3 β and decreases the phosphorylation of β -catenin. Then, the nuclear translocation of β -catenin is decreased and the transcription of cyclin D1 gene is increased.

Figure.1

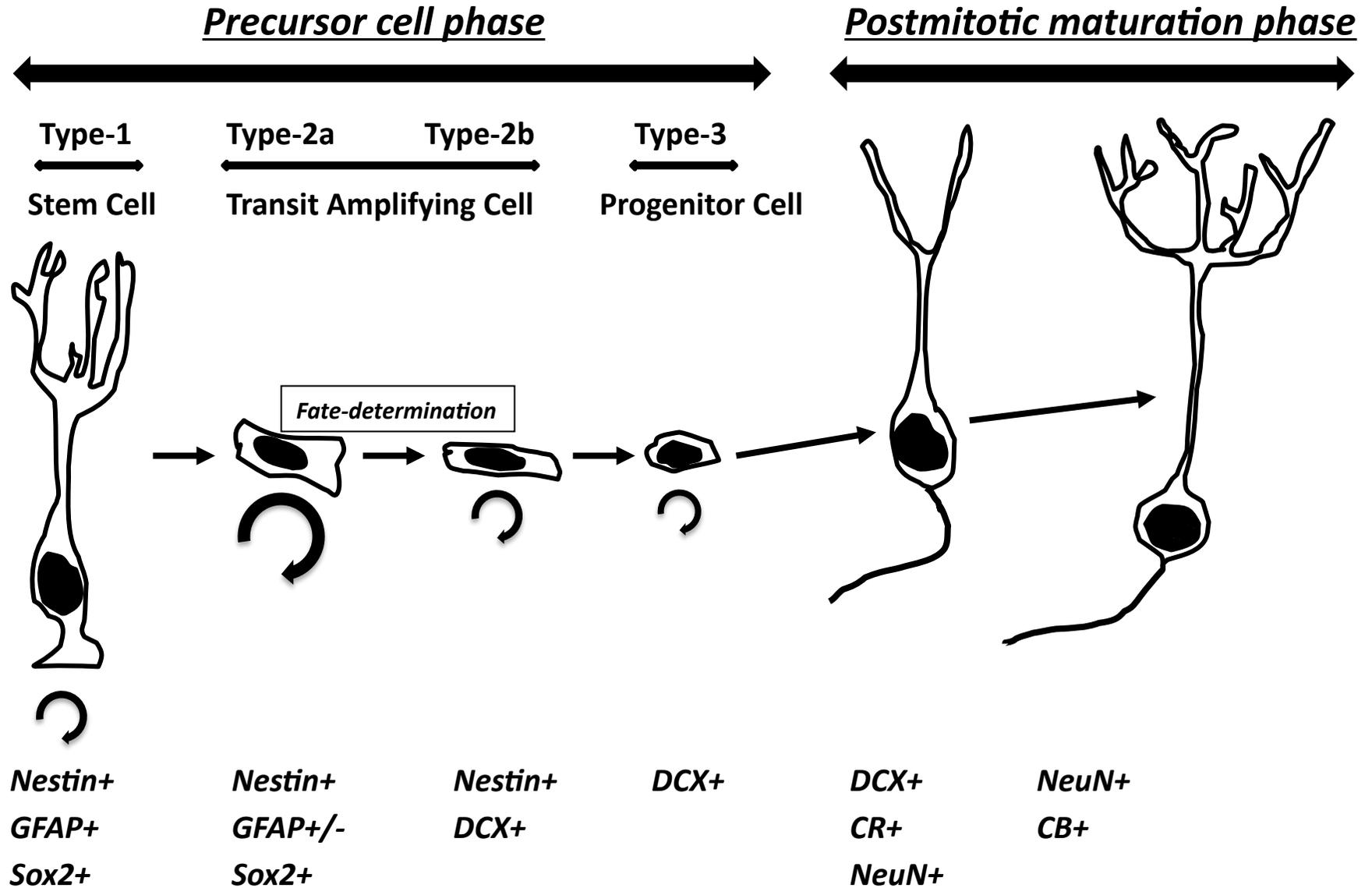


Figure.2

