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PERSPECTIVE

The effects of stress on brain and adrenal stem cells

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The brain and adrenal are critical control centers that maintain body homeostasis under basal and stress conditions, and orchestrate the body's response to stress. It is noteworthy that patients with stress-related disorders exhibit increased vulnerability to mental illness, even years after the stress experience, which is able to generate long-term changes in the brain's architecture and function. High levels of glucocorticoids produced by the adrenal cortex of the stressed subject reduce neurogenesis, which contributes to the development of depression. In support of the brain–adrenal connection in stress, many (but not all) depressed patients have alterations in the components of the limbic-hypothalamic-pituitary-adrenal (LHPA) axis, with enlarged adrenal cortex and increased glucocorticoid levels. Other psychiatric disorders, such as post-traumatic stress disorder, bipolar disorder and depression, are also associated with abnormalities in hippocampal volume and hippocampal function. In addition, hippocampal lesions impair the regulation of the LHPA axis in stress response. Our knowledge of the functional connection between stress, brain function and adrenal has been further expanded by two recent, independent papers that elucidate the effects of stress on brain and adrenal stem cells, showing similarities in the way that the progenitor populations of these organs behave under stress, and shedding more light into the potential cellular and molecular mechanisms involved in the adaptation of tissues to stress.

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The central dogma of neuroscience posited that the adult mammalian brain is incapable of generating new neurons.[1] Although evidence against this doctrine has existed since the 1960s,[2] it has been only in recent years that we accept as established knowledge the fact that the adult mammalian brain is capable of neurogenesis. This realization has opened many new research avenues, including in new approaches for neurodegenerative disease therapy. It has also given rise to new concepts in terms of the plasticity of the brain and the way it communicates with other organs. For example, stress has emerged as a powerful regulator of neurogenesis, suggesting novel means by which the endocrine system may be able to regulate brain plasticity. Elucidating the mechanisms by which the brain and the adrenal glands coordinate these complex tasks may lead us towards improved treatments for patients with stress-related disorders. We discuss reports that demonstrate how stress regulates progenitor cells in the brain and adrenal,[3,4] and note similarities between the progenitor cell systems of these two organs. Studying the progenitor cell populations of the brain and adrenal may be an essential task for the advancement of our understanding of stress and its effects on the endocrine system, neuroendocrine regulation and brain plasticity.

ADULT NEUROGENESIS

In the adult brain, neural stem cells (NSCs) convincingly able to contribute to neurogenesis reside in two well-defined germinal areas: the ventricular-subventricularzone (V-SVZ) and the subgranular zone (SGZ) in the dentate gyrus of the hippocampus. These cells share features with glial cells, including astrocytes and radial glia, such as the expression of GFAP and S100b, among others. NSCs also express the intermediate filament protein nestin, as well as vimentin and brain lipid-binding protein, which are also expressed by reactive astrocytes, activated by injury, for example.[5–8] Despite the similarities in marker expression between NSCs and glial cells, cell culture and *in vivo* tracing experiments demonstrate that they have the hallmarks of multipotent stem cells, namely the ability to self-renew and the ability to clonally generate neurons, astrocytes and oligodendrocytes.[9]

The V-SVZ and SGZ are the most established neurogenic areas. In the V-SVZ, NSCs generate neurons that migrate to the olfactory bulb.[10] In the hippocampal SGZ, the radial glia-like NSCs give rise to new dentate granule neurons, and consequently contributing to memory and cognitive functions, as well as to the processing of emotions and the regulation of stress responses.[11–14] Owing to its prominent involvement in stress responses, we will, in this article, focus on the hippocampal SGZ.

THE ADRENAL GLAND

The adrenal is composed of two different endocrine tissues: the adrenal cortex and the adrenal medulla, derived from two distinct embryonic origins, the mesoderm and the ectodermic neural crest, respectively.[15] Through the release of distinct hormones they regulate homeostasis. The mammalian adrenal cortex predominantly produces steroid hormones, of which glucocorticoids constitute a major group. The catecholamines epinephrine and norepinephrine are the major secretory products of the adrenal medulla. Despite the distinct origin and hormone production profiles, the communication between the cortex and medulla is important to the proper function of the gland and to its

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adaptation to stress. For example, early studies by Wurtman and Axelrod[16,17] demonstrated that the biosynthesis of adrenomedullary epinephrine is regulated by adrenocortical glucocorticoids. Medulla-to-cortex regulation is now also accepted to occur via paracrine control by adrenomedullary chromaffin cells.[18,19]

Adrenocortical glucocorticoids are the most widely studied adrenal product with clear effects on brain function. These have a major role in stress responses, in the context of basal and stress-related homeostasis.[20] The glucocorticoid receptor (GR) is expressed in almost all mammalian cells and mediates the transcription of genes involved in development, and the control of metabolism and immune responses.[20] Specifically, GR is expressed in several areas of the adult brain such as the hypothalamus, pituitary, hippocampus and amygdala, centers involved in glucocorticoid feedback. Of these, the hypothalamus and pituitary are primarily responsible for the maintenance of body homeostasis, whereas the other two areas are involved in memory and fear control, essential to ensuring survival.

Just as it is the case for the adult brain, the adult adrenal gland also contains a population of immature cells. In the medulla, chromaffin progenitor cells have been described and demonstrated to have the ability to self-renew in culture and differentiate into hormone-producing chromaffin cells.[3,21–26] In the adrenal cortex, a distinct population of progenitor cells exists beneath the adrenal capsule. The potential role of these cells in adaptation to stress is becoming an important new focus in the field of endocrinology.

BRAIN AND ADRENAL GLANDS: CO-WORKERS IN STRESS

The ability of an organism to adapt to stresses that are normally encountered throughout its lifespan involves the sympathoadrenal system and the limbic-hypothalamic-pituitary-adrenal (LHPA); interactions between these two systems have a central role in adaptation.[19,27] For example, the pituitary gland contains a recently identified population of stem cells that are capable of contributing to all hormone-secreting lineages.[28,29] Physiological stimuli elicit a response in these cells to enable adaptation to immediate demand; in severe experimental models, such as following adrenalectomy, a transient wave of mitoses is initiated in the pituitary gland and uncommitted stem cells are activated to preferentially generate terminally differentiated adrenocorticotropic hormone-secreting corticotrophs.[30,31] In some severe stress contexts, the sympathoadrenal and LHPA systems intercept at the level of the adrenal gland where interactions between the adrenal cortex (a component of the LHPA axis) and the adrenal medulla (a component of the sympathoadrenal neuroendocrine system) are key in terms of adaptation.[27,32]

The brain and adrenal are critical control centers that maintain body homeostasis under basal and stress conditions, and orchestrate the body's response to stress. It is noteworthy that patients with stress-related disorders exhibit increased vulnerability to mental illness, even years after the stress experience, which is able to generate long-term changes in the brain's architecture and function. As mentioned above, high levels of glucocorticoids produced by the adrenal cortex of the stressed subject reduce neurogenesis, which contributes to the development of depression.[33] In support of the brain–adrenal connection in stress, many (but not all) depressed patients have alterations in the components of the LHPA axis, with enlarged adrenal cortex and increased glucocorticoid levels.[34,35] Other psychiatric disorders, such as post-traumatic stress disorder, bipolar disorder and depression, are associated with abnormalities in hippocampal volume and hippocampal function.[36–38] In addition, hippocampal lesions impair the regulation of the LHPA axis in stress response.[39,40]

After experimental adrenalectomy, the number of astrocytes in the SGZ increased within 1 week,[41] and after 1 month the number of granular cell layer (GCL) neurons in the dentate gyrus of the hippocampus also increased.[42,43] Under normal conditions, adrenal steroids induce extracellular glutamate accumulation in the GCL; following adrenalectomy, extracellular levels of glutamate decreased. Variations in glutamate levels could be detected by astrocytes thus affecting their behavior.[44] Hippocampal astrocytes express the mineralocorticoid and GRs, offering another possible mechanism by which glial function may be regulated by the adrenal.[45]

Acute, mild stress has been shown to induce hippocampal neurogenesis, which itself is required for proper stress responses.[46] However, intense stress such as that induced in chronically stressed animals has been demonstrated to have a vastly negative impact on neurogenesis in the hippocampus. This is mainly due to the high concentrations of stress hormones, which were shown to possess a catabolic function and growth-inhibiting effects. More specifically, glucocorticoids suppress cell proliferation and promote cell death in several cell types.[47–49] The hippocampus is densely populated with receptors for stress hormones,[45] suggesting that one role of these hormones in the adult brain is to regulate the production of new neurons by inhibiting neurogenesis in the dentate gyrus of the hippocampus.[50] In particular, rodents subjected to chronic restraint conditions exhibited a reduced number of proliferating cells; the population of doublecortin-positive cells, the newly formed neurons, was reduced in the dentate gyrus.[51] At least in part, the reduction was allocated to impaired cell survival and resulted in a reduction in the number of granule cells in the hippocampus.[52]

The brain and the adrenal medulla share several features. Thus, the adrenal medulla, one of the most intensively studied of the neural crest derivatives, was even described as the 'peripheral brain',[15] mainly because of the morphological and functional neuron-like characteristics of chromaffin cells, the main adrenomedullary cell population. Chromaffin cells, such as neurons, are secretory cells that release their secretory products upon electrical and chemical inputs, and provide for rapid communication between widely separated parts of the body. On the basis of these similarities between the major cell types of the two tissues, it can be hypothesized that also the plastic and regenerative potential of these tissues resides in a similar type of stem cell, especially when considering that both tissues share the same ectodermic origin.

TWO COMPLEMENTARY DATA SETS ELUCIDATE THE EFFECTS OF STRESS ON BRAIN AND ADRENAL STEM CELLS

There is now strong evidence that nestin+ cells in the adult brain and adrenal medulla behave as progenitors presented in two independent, but conceptually complementary, papers. Chetty *et al*. [4] used lineage tracing methods, utilizing a nestin-CreER/YFP inducible reporter mouse line, to demonstrate that nestin+ cells in the adult brain can give rise to oligodendrocytes and neurons. Whether the nestin+ cells that generated oligodendrocytes in the hippocampus were themselves located in the hippocampus is not easy to determine in such *in vivo* experiments; however, the ability of adult hippocampal NSC cultures (which are generally nestin+) to generate oligodendrocytes may support this possibility. Rubin de Celis *et al*.[3] independently used a different but similar mouse strain (nestin-Cre ERT/RosaYFP) to demonstrate that nestin+ cells in the adult adrenal medulla can generate chromaffin cells. In addition, they used a nestin-GFP reporter to count nestin+ cells *in vivo* and to demonstrate the proliferative ability of nestin+ cells when placed in culture. Put together, these two papers demonstrate that nestin+ cells in the brain and adrenal have progenitor cell properties.

Both labs used similar immobilization stress models to assess changes in the function of nestin+ cells that may contribute to our molecular and cellular understanding of stress adaptation in their

respective organs. Chetty *et al*. used a rat model that involved daily consecutive periods of immobilization over 7 days. They reported an increase in the percentage of proliferating cells (BrdU+ labeled) that express the oligodendrocyte markers myelin basic protein (MBP) and receptor interacting protein (RIP), at the hippocampal dentate gyrus.

Rubin de Celis *et al*. also reported an increase in the number of nestin+ cells (using a nestin-GFP reporter mouse line) following a 1-day stress session. This results in the adrenal medulla mirrors the data reported by Chetty *et al*. from the brain, suggesting that both organs respond to forms of stress by increasing the population of progenitors. However, after the first day increase in adrenomedullary nestin+ cells, their number decreased, eventually (at day 7 of daily stress sessions) reaching levels below non-stressed baseline. Despite the reduction in nestin+ cell number at day 7, the percentage of nestin+ cells in the adrenal medulla at day 7 that is in a proliferative state (EdU labeled) increased. These results may suggest depletion (temporary or permanent is not clear, at this point) of nestin+ cells in the adrenal. It may be interesting to address whether similar reduction may be observed also in the brain, perhaps at time points greater than 7 days.

Possible nestin+ cell depletion may be attributed to differentiation of nestin+ cells. To follow the fate of nestin+ cells, both groups used inducible nestin-Cre mouse lines. More specifically, they addressed changes in the fate specification potential of nestin+ cells in stress paradigms. Chetty *et al*. used a model where mice were administered with the glucocorticoid corticosterone (a mediator of stress responses); in addition, they employed the rat immobilization model that does not allow for lineage tracing, but allows the assessment of the proliferative state of different cell types. Rubin de Celis *et al*. used the immobilization model in mice allowing the lineage tracing of nestin+ cells.

In the adult rat brain, immobilization-induced stress reduced neurogenesis and increased oligodendrogliogenesis (data were obtained by counting BrdU+/TUJ1+ and BrdU+/MBP+, and BrdU+/RIP+ cells). This prompted the authors to address two questions. First, whether the observed stress response was mediated by glucocorticoids. For this, the authors utilized the mouse model of corticosterone administration (mice were given 10 daily injections and the brain were assessed 7 days after that) and followed up their studies with *in vitro* experiments where hippocampal NSCs were treated with corticosterone. Second, they addressed the effect of corticosterone on the differentiation competence of nestin+ cells *in vivo*. The inducible nestin-Cre reporter mouse line was employed for these experiments. The results showed that, like with the rat immobilization/restraint model, glucocorticoid treatment *in vivo* in mice also reduced neurogenesis and increased oligodendrogliogenesis. The results were confirmed *in vitro* where corticosterone treatment of adult hippocampal NSCs reduced neurogenesis and increased oligodendrocyte generation in a GR–mediated manner (this was demonstrated by opposing the corticosterone effects when the cells were transfected with a dominant-negative GR viral vector). Additional experiments with synthetic glucocorticoid and GR agonist dexamethasone confirmed these observations. The results demonstrated that both neurons and oligodendrocytes in the hippocampus can be generated by nestin+ cells, and that corticosterone decreases neurogenesis, whereas it increases oligodendrogliogenesis.

In the adrenal medulla of stressed animals, a greater number of nestin+ cell–derived chromaffin cells was reported (at the end of the 1-week stress period). This result, in combination with the decreased nestin-GFP cell number may represent depletion of the nestin+ cell population as it differentiates into chromaffin cells. In support of this, following stress, mice that were placed back under normal (non-stressful) conditions for 1 week reinstated the number of nestin-GFP labeled cells to normal values. Chetty *et al*. also addressed the question of depletion in adult rats *in vivo* by allowing the rats to recover for 1 week after the end of the corticosterone administration period. They reported the reinstatement of the number of newly generated neurons to normal levels. However, the percentage of newly born oligodendrocytes remained higher in the corticosterone-treated rats.

In vitro experiments using the inducible nestin mouse model confirmed the multipotential nature of adrenomedullary progenitor cells by showing that they can generate the three major lineages of the adrenal medulla: glia, neurons and chromaffin cells. It should be noted that the cell culture medium used contains the supplement B27, which contains glucocorticoids and this may have affected the exact fate specification. Future experiments performed in the absence of glucocorticoids may quantitatively address the potential of these cells.

In conclusion, these two papers reveal further effects of stress on the cellular architecture of the brain and adrenal medulla. They show similarities in the way that the progenitor populations of these organs behave under stress, shedding more light into the potential cellular and molecular mechanisms involved in the adaptation of tissues to stress.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1 Berciano J, Lafarga M, Berciano M. Santiago Ramon y Cajal. *Neurologia* 2001; **16**: 118–121.
2 Altman J. Are new neurons formed in the brains of adult mammals? *Science* 1962; **135**: 1127–1128.
3 Rubin de Celis MF, Garcia-Martin R, Wittig D, Valencia GD, Enikolopov G, Funk RH *et al.* Multipotent glia-like stem cells mediate stress adaptation. *Stem Cells* 2015; **33**: 2037–2051.
4 Chetty S, Friedman AR, Taravosh-Lahn K, Kirby ED, Mirescu C, Guo F *et al.* Stress and glucocorticoids promote oligodendrogenesis in the adult hippocampus. *Mol Psychiatry* 2014; **19**: 1275–1283.
5 Malatesta P, Hartfuss E, Gotz M. Isolation of radial glial cells by fluorescent-activated cell sorting reveals a neuronal lineage. *Development* 2000; **127**: 5253–5263.
6 Doetsch F, Caille I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. *Cell* 1999; **97**: 703–716.
7 Fuentealba LC, Obernier K, Alvarez-Buylla A. Adult neural stem cells bridge their niche. *Cell Stem Cell* 2012; **10**: 698–708.
8 Robel S, Berninger B, Gotz M. The stem cell potential of glia: lessons from reactive gliosis. *Nat Rev Neurosci* 2011; **12**: 88–104.
9 Malatesta P, Gotz M. Radial glia - from boring cables to stem cell stars. *Development* 2013; **140**: 483–486.
10 Kriegstein A, Alvarez-Buylla A. The glial nature of embryonic and adult neural stem cells. *Annu Rev Neurosci* 2009; **32**: 149–184.
11 Bonaguidi MA, Song J, Ming GL, Song H. A unifying hypothesis on mammalian neural stem cell properties in the adult hippocampus. *Curr Opin Neurobiol* 2012; **22**: 754–761.
12 Zhao C, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. *Cell* 2008; **132**: 645–660.
13 Fanselow MS, Dong HW. Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron* 2010; **65**: 7–19.
14 Eckenhoff MF, Rakic P. Radial organization of the hippocampal dentate gyrus: a Golgi, ultrastructural, and immunocytochemical analysis in the developing rhesus monkey. *J Comp Neurol* 1984; **223**: 1–21.
15 Bornstein SR, Ehrhart-Bornstein M, Androutsellis-Theotokis A, Eisenhofer G, Vukicevic V, Licinio J *et al.* Chromaffin cells: the peripheral brain. *Mol Psychiatry* 2012; **17**: 354–358.
16 Wurtman RJ, Axelrod J. Adrenaline synthesis: control by the pituitary gland and adrenal glucocorticoids. *Science* 1965; **150**: 1464–1465.
17 Wurtman RJ, Axelrod J. Control of enzymatic synthesis of adrenaline in the adrenal medulla by adrenal cortical steroids. *J Biol Chem* 1966; **241**: 2301–2305.
18 Ehrhart-Bornstein M, Hinson JP, Bornstein SR, Scherbaum WA, Vinson GP. Intraadrenal interactions in the regulation of adrenocortical steroidogenesis. *Endocr Rev* 1998; **19**: 101–143.

19 Ehrhart-Bornstein M, Bornstein SR. Cross-talk between adrenal medulla and adrenal cortex in stress. *Ann N Y Acad Sci* 2008; **1148**: 112–117.
20 Kino T. Glucocorticoid receptor. In: De Groot LJ, Beck-Peccoz P, Chrousos G (eds). Endotext [Internet]. MDText.com, Inc.: South Dartmouth, MA, 2000–2013. Available at http://www.ncbi.nlm.nih.gov/books/NBK279171/.
21 Vukicevic V, Schmid J, Hermann A, Lange S, Qin N, Gebauer L *et al*. Differentiation of chromaffin progenitor cells to dopaminergic neurons. *Cell Transplant* 2012; **21**: 2471–2486.
22 Vukicevic V, Rubin de Celis MF, Pellegata NS, Bornstein SR, Androutsellis-Theotokis A, Ehrhart-Bornstein M. Adrenomedullary progenitor cells: Isolation and characterization of a multi-potent progenitor cell population. *Mol Cell Endocrinol* 2015; **408**: 178–184.
23 Vukicevic V, Qin N, Balyura M, Eisenhofer G, Wong ML, Licinio J *et al*. Valproic acid enhances neuronal differentiation of sympathoadrenal progenitor cells. *Mol Psychiatry* 2015; **20**: 941–950.
24 Santana MM, Chung KF, Vukicevic V, Rosmaninho-Salgado J, Kanczkowski W, Cortez V *et al*. Isolation, characterization, and differentiation of progenitor cells from human adult adrenal medulla. *Stem Cells Transl Med* 2012; **1**: 783–791.
25 Chung KF, Sicard F, Vukicevic V, Hermann A, Storch A, Huttner WB *et al*. Isolation of neural crest derived chromaffin progenitors from adult adrenal medulla. *Stem Cells* 2009; **27**: 2602–2613.
26 Saxena S, Wahl J, Huber-Lang MS, Stadel D, Braubach P, Debatin KM *et al*. Generation of murine sympathoadrenergic progenitor-like cells from embryonic stem cells and postnatal adrenal glands. *PLoS One* 2013; **8**: e64454.
27 Goldstein DS. Adrenal responses to stress. *Cell Mol Neurobiol* 2010; **30**: 1433–1440.
28 Andoniadou CL, Gaston-Massuet C, Reddy R, Schneider RP, Blasco MA, Le Tissier P *et al*. Identification of novel pathways involved in the pathogenesis of human adamantinomatous craniopharyngioma. *Acta Neuropathol* 2012; **124**: 259–271.
29 Andoniadou CL, Matsushima D, Mousavy Gharavy SN, Signore M, Mackintosh AI, Schaeffer M *et al*. Sox2(+) stem/progenitor cells in the adult mouse pituitary support organ homeostasis and have tumor-inducing potential. *Cell Stem Cell* 2013; **13**: 433–445.
30 Nolan LA, Levy A. A population of non-luteinising hormone/non-adrenocorticotrophic hormone-positive cells in the male rat anterior pituitary responds mitotically to both gonadectomy and adrenalectomy. *J Neuroendocrinol* 2006; **18**: 655–661.
31 Rizzoti K, Akiyama H, Lovell-Badge R. Mobilized adult pituitary stem cells contribute to endocrine regeneration in response to physiological demand. *Cell Stem Cell* 2013; **13**: 419–432.
32 Goldstein DS. Concepts of scientific integrative medicine applied to the physiology and pathophysiology of catecholamine systems. *Compr Physiol* 2013; **3**: 1569–1610.
33 Gold PW. The organization of the stress system and its dysregulation in depressive illness. *Mol Psychiatry* 2015; **20**: 32–47.
34 Kessing LV, Willer IS, Knorr U. Volume of the adrenal and pituitary glands in depression. *Psychoneuroendocrinology* 2011; **36**: 19–27.
35 Nemeroff CB, Krishnan KR, Reed D, Leder R, Beam C, Dunnick NR. Adrenal gland enlargement in major depression. A computed tomographic study. *Arch Gen Psychiatry* 1992; **49**: 384–387.
36 Karl A, Schaefer M, Malta LS, Dorfel D, Rohleder N, Werner A. A meta-analysis of structural brain abnormalities in PTSD. *Neurosci Biobehav Rev* 2006; **30**: 1004–1031.
37 Kitayama N, Vaccarino V, Kutner M, Weiss P, Bremner JD. Magnetic resonance imaging (MRI) measurement of hippocampal volume in posttraumatic stress disorder: a meta-analysis. *J Affect Disord* 2005; **88**: 79–86.
38 Frey BN, Andreazza AC, Nery FG, Martins MR, Quevedo J, Soares JC *et al*. The role of hippocampus in the pathophysiology of bipolar disorder. *Behav Pharmacol* 2007; **18**: 419–430.
39 Jacobson L, Sapolsky R. The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. *Endocr Rev* 1991; **12**: 118–134.
40 Dedovic K, Duchesne A, Andrews J, Engert V, Pruessner JC. The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. *Neuroimage* 2009; **47**: 864–871.
41 Lois C, Alvarez-Buylla A. Proliferating subventricular zone cells in the adult mammalian forebrain can differentiate into neurons and glia. *Proc Natl Acad Sci USA* 1993; **90**: 2074–2077.
42 Chen G, Rajkowska G, Du F, Seraji-Bozorgzad N, Manji HK. Enhancement of hippocampal neurogenesis by lithium. *J Neurochem* 2000; **75**: 1729–1734.
43 Cameron HA, Gould E. Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. *Neuroscience* 1994; **61**: 203–209.
44 Woolley CS, McEwen BS. Estradiol regulates hippocampal dendritic spine density via an N-methyl-D-aspartate receptor-dependent mechanism. *J Neurosci* 1994; **14**: 7680–7687.
45 Banasr M, Hery M, Brezun JM, Daszuta A. Serotonin mediates oestrogen stimulation of cell proliferation in the adult dentate gyrus. *Eur J Neurosci* 2001; **14**: 1417–1424.
46 Snyder JS, Soumier A, Brewer M, Pickel J, Cameron HA. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. *Nature* 2011; **476**: 458–461.
47 McConkey DJ, Nicotera P, Hartzell P, Bellomo G, Wyllie AH, Orrenius S. Glucocorticoids activate a suicide process in thymocytes through an elevation of cytosolic Ca2+ concentration. *Arch Biochem Biophys* 1989; **269**: 365–370.
48 Chen TL. Inhibition of growth and differentiation of osteoprogenitors in mouse bone marrow stromal cell cultures by increased donor age and glucocorticoid treatment. *Bone* 2004; **35**: 83–95.
49 te Pas MF, de Jong PR, Verburg FJ. Glucocorticoid inhibition of C2C12 proliferation rate and differentiation capacity in relation to mRNA levels of the MRF gene family. *Mol Biol Rep* 2000; **27**: 87–98.
50 Mirescu C, Gould E. Stress and adult neurogenesis. *Hippocampus* 2006; **16**: 233–238.
51 Yun J, Koike H, Ibi D, Toth E, Mizoguchi H, Nitta A *et al*. Chronic restraint stress impairs neurogenesis and hippocampus-dependent fear memory in mice: possible involvement of a brain-specific transcription factor Npas4. *J Neurochem* 2010; **114**: 1840–1851.
52 Pham K, Nacher J, Hof PR, McEwen BS. Repeated restraint stress suppresses neurogenesis and induces biphasic PSA-NCAM expression in the adult rat dentate gyrus. *Eur J Neurosci* 2003; **17**: 879–886.