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Role of adult hippocampal neurogenesis in stress resilience

Brunno R. Levone [a], John F. Cryan [a, b, **], Olivia F. O'Leary [a, b, *]

[a] Department of Anatomy and Neuroscience, University College Cork, Ireland
[b] Alimentary Pharmabiotic Centre, University College Cork, Ireland

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ABSTRACT

There is a growing appreciation that adult hippocampal neurogenesis plays a role in emotional and cognitive processes related to psychiatric disorders. Although many studies have investigated the effects of stress on adult hippocampal neurogenesis, most have not focused on whether stress-induced changes in neurogenesis occur specifically in animals that are more resilient or more susceptible to the behavioural and neuroendocrine effects of stress. Thus, in the present review we explore whether there is a clear relationship between stress-induced changes in adult hippocampal neurogenesis, stress resilience and antidepressant-induced recovery from stress-induced changes in behaviour. Exposure to different stressors is known to reduce adult hippocampal neurogenesis, but some stressors have also been shown to exert opposite effects. Ablation of neurogenesis does not lead to a depressive phenotype, but it can enhance responsiveness to stress and affect stress susceptibility. Monoaminergic-targeted antidepressants, environmental enrichment and adrenalectomy are beneficial for reversing stress-induced changes in behaviour and have been shown to do so in a neurogenesis-dependant manner. In addition, stress and antidepressants can affect hippocampal neurogenesis, preferentially in the ventral hippocampus. Together, these data show that adult hippocampal neurogenesis may play a role in the neuroendocrine and behavioural responses to stress, although it is not yet fully clear under which circumstances neurogenesis promotes resilience or susceptibility to stress. It will be important that future studies carefully examine how adult hippocampal neurogenesis can contribute to stress resilience/susceptibility so that it may be appropriately exploited for the development of new and more effective treatments for stress-related psychiatric disorders.

1. Introduction

"It is not stress that kills us, it is our reaction to it".

Hans Selye

Stress is an event that threatens the homeostasis of the organism and as a result causes physiological and behavioural responses that attempt to reinstate equilibrium (McEwen and Wingfield, 2003; de Kloet et al., 2005; Day, 2005). Allostasis can be defined as the collection of processes that are required to achieve internal and external stability in the face of a changing environment thus maintaining homeostasis (McEwen and Wingfield, 2003; de Kloet et al., 2005; Day, 2005). Allostatic load results from excessive stress or a failure to achieve homeostasis and may occur as a result of repeated stress from multiple stressors, poor adaptation and prolonged or inadequate response to stress (McEwen, 2007; McEwen and Stellar, 1993). While the acute stress response is an important and necessary mechanism to adapt to environmental changes that occur throughout life thus promoting effective coping, severe or chronic stress can result in allostatic load and it is also a contributing risk factor for the development of several psychiatric disorders such as depression and post-traumatic stress disorder (PTSD) (McEwen and Wingfield, 2003; McEwen, 2007). However, it is also important to note that many stress-exposed individuals do not develop stress-related psychiatric disorders (Charney and Manji, 2004; Yehuda and LeDoux, 2007; Caspi et al., 2003) and are thus more resilient to the negative consequences of stress than others. Resilience to stress is the ability to cope with environmental

* Corresponding author. Department of Anatomy and Neuroscience, University College Cork, Rm 4.10, Western Gateway Building, Ireland. Tel.: +353 21 420 5480; fax: +353 21 4273518.
** Corresponding author. Department of Anatomy and Neuroscience, University College Cork, Ireland. Tel.: +353 21 420 5426; fax: +353 21 4273518.
E-mail addresses: j.cryan@ucc.ie (J.F. Cryan), o.oleary@ucc.ie (O.F. O'Leary).

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challenges, ensuring survival, while susceptibility to the negative consequences of stress seems to result from an improper functioning of the systems of resilience or an amplification of the stress experience (Karatsoreos and McEwen, 2013), which in turn can result in maladaptive physiological and behavioural responses. Such maladaptive responses to stress may increase the risk for the development of stress-related psychiatric disorders, and as such great effort is being made to elucidate the neural processes that underlie stress-resilience in the hope that these might be then exploited for drug development (Franklin Tamara et al., 2012; Russo et al., 2012; Wu et al., 2013; Hughes, 2012).

1.1. The hippocampus & stress

The hippocampus is a key brain area involved in the regulation of the stress response, exerting negative feedback on the hypothalamic–pituitary–adrenal (HPA) axis (Jacobson and Sapolsky, 1991), the system within the body responsible for the release of glucocorticoid stress hormones. Stressors rapidly stimulate the secretion of corticotropin-releasing factor and vasopressin from parvocellular neurons of the paraventricular nucleus of the hypothalamus and this stimulates the release of adrenocorticotropic hormone from the anterior pituitary, which in turn stimulates the release of glucocorticoid stress hormones from the adrenal cortex into the circulation (Cullinan et al., 1995). These glucocorticoids, cortisol in humans and corticosterone in rodents (Herman and Cullinan, 1997), feedback onto two types of receptors in the brain: the mineralocorticoid receptors (MR) and glucocorticoid receptors (GR), which are highly expressed in limbic structures of the brain, including the hippocampus (Morimoto et al., 1996). While hippocampal MR mediates the effects of glucocorticoids on assessment of the stressor and initiation of the stress response, GR acts in the consolidation of acquired information (de Kloet et al., 2005; De Kloet et al., 1998). Following stress termination, glucocorticoid concentrations slowly decrease to pre-stress levels and this recovery is primarily controlled by negative feedback of glucocorticoids onto their receptors in the anterior pituitary and the paraventricular nucleus of the hypothalamus (Herman and Cullinan, 1997; De Kloet et al., 1998). Activation of these receptors in the hippocampus also exerts negative feedback on the HPA axis, suppressing further release of glucocorticoids following stress termination, thus inappropriate functioning of the hippocampus could disrupt proper functioning of the HPA axis (De Kloet et al., 1998). In addition to playing a key role in the regulation of stress response, the hippocampus is also particularly vulnerable to the effects of stress (McEwen and Sapolsky, 1995; McEwen et al., 1992; Sapolsky, 1986). Plasma concentrations of cortisol are often increased in depressed adults (Westrin et al., 1999) and it has been suggested that elevated glucocorticoid concentrations contribute to stress-induced atrophy of the hippocampus (McEwen and Sapolsky, 1995) and its correlation with cognitive dysfunction (Lupien et al., 1998). Accordingly, neuroimaging studies report volumetric reductions in the hippocampus in depression (Bremner et al., 2000; Frodl et al., 2002; Sheline et al., 1996; Videbech and Ravnkilde, 2004) and that these volumetric reductions seem to be more apparent in unmedicated depressed individuals (Sheline et al., 2003) and in poor responders to antidepressant treatments (Frodl et al., 2008). Similarly, volumetric reductions in the hippocampus have also been reported in PTSD patients (Felmingham et al., 2009; Smith, 2005; Bremner et al., 2003) and PTSD patients exhibit dysfunction of the HPA-axis with high levels of corticotropin-releasing hormone in the cerebrospinal fluid (Bremner et al., 1997) and low levels of cortisol in urine (Yehuda et al., 1995), indicating an enhanced HPA-axis feedback regulation (de Kloet et al., 2006). Taken together, it is clear that there is a reciprocal relationship between the hippocampus and glucocorticoids and that disrupted HPA-axis activity might impact hippocampal structure and function which in turn might further impact hippocampal regulation of glucocorticoid concentrations.

1.2. The hippocampus & neurogenesis

In addition to its role in regulating the HPA axis, the hippocampus is a rather unique structure in that it is one of just a few areas in the healthy mammalian brain where neurogenesis, the birth of new neurons, occurs throughout adult life (Kempermann et al., 2004; Ming and Song, 2011). Adult hippocampal neurogenesis occurs in the subgranular zone of the hippocampus and is comprised of several stages: cell proliferation, neuronal differentiation and survival, and maturation of the newly-born neurons (Christie and Cameron, 2006) (see Fig. 1). It is now well established that adult hippocampal neurogenesis is sensitive to a number of extrinsic factors including stress, antidepressant treatment and environmental experience (Schloesser et al., 2010; Tanti et al., 2012; Simon et al., 2005; Gould et al., 1997; Kempermann et al., 1997; Malberg et al., 2000). Chronic stress during adulthood has been shown to decrease all stages of adult hippocampal neurogenesis (Simon et al., 2005; Jayatissa et al., 2006, 2009; Lehmann et al., 2013; Mitra et al., 2006; Dranovsky and Hen, 2006; Schoenfeld and Gould, 2012), an effect reversible by chronic antidepressant treatments (Dranovsky and Hen, 2006; Tanti and Belzung, 2013; Malberg and Duman, 2003; Sahay and Hen, 2007).

1.3. Stress & hippocampal neurogenesis

Accumulating evidence suggests that exposure to stress during the prenatal or early postnatal (early-life stress) periods leads to alterations in hippocampal neurogenesis and the stress response during adult life. Prenatal stress may influence adult phenotypes and early-life stress has been implicated in susceptibility to depression and anxiety in later life (Seckl and Holmes, 2007). Accordingly, the exposure of pregnant animals to stress or glucocorticoids may affect fetal brain development of the offspring (Brummelte et al., 2006; Lucassen et al., 2009) and it may also lead to anxiety and depressive behaviour, increased HPA axis activity, memory impairment (Fenoglio et al., 2006; Henry et al., 1994; Vallee et al., 1997) as well as reduced hippocampal neurogenesis in both rodents (Lucassen et al., 2009; Lemaire et al., 2000; Mandyam et al., 2008) and non-human primates (Coe et al., 2003) later in adult life. Importantly, these changes induced by prenatal stress may depend upon the genetic background (Lucassen et al., 2009; Bosch et al., 2006), thus highlighting that gene–environment interactions may modulate adult hippocampal neurogenesis and as well as susceptibility and resilience to stress. Similarly, adverse experience in early postnatal life, such as maternal separation, can reduce adult hippocampal neurogenesis (Kikusui et al., 2009; Lajud et al., 2012; Mirescu et al., 2004), although these effects may be sex-dependent as one study reported decreases in females but increases in male rats (Oomen et al., 2009). Maternally separated pups can exhibit decreased hippocampal cell proliferation in adulthood (Mirescu et al., 2004) and active maternal care is important for reducing HPA axis responsiveness and increasing glucocorticoid feedback sensitivity, leading to stress resilience (Liu et al., 1997; Plotsky and Meaney, 1993). In addition to prenatal and early life stress protocols, exposure to stressors in adult life have also been shown to decrease adult hippocampal neurogenesis, including chronic restraint (Luo et al., 2005; Rosenbrock et al., 2005; Snyder et al., 2011), chronic unpredictable mild stress (Jayatissa et al., 2006, 2009; Surget et al., 2011), social defeat stress (Schloesser et al.,

2010; Simon et al., 2005), and others (see Table 1). Furthermore, chronic corticosterone treatment, which is used as a model of HPA axis overactivity, has also been shown to decrease adult hippocampal neurogenesis (Brummelte and Galea, 2010; Ekstrand et al., 2008).

Like humans, animals vary in their individual behavioural responses to stress such that stress paradigms can produce cohorts of animals that can be classified as either stress-susceptible or stress-resilient, depending upon their behavioural response to stress (Krishnan et al., 2007; Feder et al., 2009). For example, chronic stress in susceptible rodents can induce depression-like behaviours such as anhedonia and social withdrawal, while such behaviours are not induced in resilient animals (Krishnan et al., 2007; Willner, 1997). Thus, animals can be segregated into subgroups of stress-resilient and stress-susceptible animals in an effort to identify the neurobiological mechanisms underlying stress resilience (Jayatissa et al., 2006; Blugeot et al., 2011; Strekalova et al., 2004; Wood et al., 2010). Interestingly, this variation in the stress response has been linked to hippocampal volumes whereby resilient animals exhibit increase hippocampal volume (by 4%), even after stress, while susceptible animals exhibit decreases in volume (by 1%) (Tse et al., 2014), findings which parallel the volumetric losses in the hippocampus of individuals with depression or PTSD (Sheline et al., 1996; Felmingham et al., 2009), both of which are stress-related disorders. However, while many studies have investigated the effects of stress on adult hippocampal neurogenesis, relatively few have determined whether stress-induced changes in adult hippocampal neurogenesis occur specifically in animals that are more resilient or more susceptible to the behavioural and neuroendocrine effects of stress.

2. Do changes in adult hippocampal neurogenesis predict susceptibility to stress-induced changes in behaviour?

While there is a general agreement that chronic stress can decrease adult hippocampal neurogenesis (Simon et al., 2005; Jayatissa et al., 2006, 2009; Lehmann et al., 2013; Mitra et al., 2006; Dranovsky and Hen, 2006; Schoenfeld and Gould, 2012; Pham et al., 2003; Perera et al., 2011; Fa et al., 2014), it is also important to note that negative findings have also been reported (Hanson et al., 2011a; Lee et al., 2006; Lyons et al., 2010; O'Leary et al., 2012; Parihar et al., 2011). While these negative findings might be stressor, species, sex or strain-dependent (Schoenfeld and Gould, 2012; Hanson et al., 2011b; Westenbroek et al., 2004; Lisowski et al., 2011), it is also important to consider that interindividual variation in the behavioural susceptibility to stress might contribute to conflicting findings. This also raises the question as to whether changes in adult hippocampal neurogenesis may predict resilience or susceptibility to stress-induced changes in behaviour. Alternatively, an individual's behavioural response to stress may be independent of the effects of stress on adult hippocampal neurogenesis. One approach to investigating the relationship between stress resilience and adult hippocampal neurogenesis is to compare neurogenesis in stress-susceptible and stress-resilient animals, although to our knowledge few studies to date have approached this question in such a manner. Given the evidence that stress decreases adult hippocampal neurogenesis in an antidepressant-reversible manner, one might expect stress-induced decreases in neurogenesis to be correlated with increased stress susceptibility. Surprisingly, however, it has been reported that the survival of cells born 24 h after stress was increased four weeks later in mice that

Table 1
Summary of the effects of animal models of prenatal, early life and adult stress on adult hippocampal neurogenesis.

Protocols of stress	Description	Decreased	No change	Increased
Prenatal				
Restraint of pregnant dams	Pregnant dams undergo daily restraint stress	Lucassen et al., 2009; Lemaire et al., 2000; Mandyam et al., 2008; Bosch et al., 2006 [a]		
Acoustic startle	Pregnant non-human primates are exposed to acoustic startle each day during either early gestation (gestational days 50–92) or late gestation (gestational days 105–147)	Coe et al., 2003		
Early life				
Maternal separation	Separation of pups from the dam, which may lead to behavioural and neuroendocrine alterations in adult life	(Kikusui et al., 2009; Lajud et al., 2012; Mirescu et al., 2004) [b] (Oomen et al., 2009)[c]		Oomen et al., 2009 [c]
Adult				
Corticosterone administration	Chronic or acute administration of the stress hormone corticosterone	Brummelte and Galea, 2010; Ekstrand et al., 2008		
Foot shock	Chronic exposure to foot shocks	Malberg and Duman, 2003 [d]	Van der Borght et al., 2005 [e]	
Repeated restraint stress	Chronic daily restraint	Luo et al., 2005; Rosenbrock et al., 2005; Snyder et al., 2011	O'Leary et al., 2012	Parihar et al., 2011
Chronic unpredictable mild stress	Chronic exposure to unpredictable and different types of stressors	Jayatissa et al., 2006; Jayatissa et al., 2009; Surget et al., 2011 [e]	Lee et al., 2006 [f]	
Social stress	Chronic exposure to an aggressive resident which induces social avoidance, anhedonia, weight loss and increases in anxiety-like behaviour	Schloesser et al., 2010; Simon et al., 2005	Hanson et al., 2011a	Lagace et al., 2010
Social stress in non-human primates	Animals are housed alone or with an unknown male			Lyons et al., 2010

[a] In some protocols (Lucassen et al., 2009; Bosch et al., 2006) pregnant dams are also exposed to an unfamiliar lactating resident (maternal defeat).
[b] In these studies, pups were separated from the dam on a daily basis for several hours per day.
[c] In this study, pups were separated from the dam just once, but for a long period of time (24 h). This reduced neurogenesis in females but increased neurogenesis in males.
[d] This study used chronic inescapable foot shock which leads to reduced attempts to escape the shock even when given the opportunity to avoid it (i.e. learned helplessness).
[e] In this study, animals were allowed to escape from the foot shock, thus the stress was controllable.
[f] Studies that showed reduced neurogenesis used the following stressors, including food/water deprivation, cage tilt, altered dark–light cycle, altered bedding, while the study that showed no changes in neurogenesis used a slightly different stress protocol, including 1 or 2 h of daily restraint, food/water deprivation, altered dark cycle, altered bedding, but no cage tilt.

were susceptible to developing social avoidance behaviour following social defeat stress, while similar effects were not observed in resilient mice (Lagace et al., 2010). The association of increased adult hippocampal neurogenesis with stress susceptibility is also supported by a study in primates that demonstrated increased neurogenesis and improvements in learning in primates housed under stressful conditions (alone or with an unknown male), versus standard conditions (with a familiar male) (Lyons et al., 2010). Thus, exposure to some protocols of stress can increase adult hippocampal neurogenesis, even in susceptible animals.

Predictability or controllability of the stressor seems to be an important determining factor of whether stress increases or decreases adult hippocampal neurogenesis (Parihar et al., 2011; Van der Borght et al., 2005). While unpredictable chronic stress increased depressive-like behaviour (Lucas et al., 2014), predictable stress, which consisted of a daily 5-min session of restraint at the same time each day, decreased anxiety and depressive behaviour and increased adult hippocampal neurogenesis (Parihar et al., 2011). Similarly, a study reported that controllable stress in the form of chronic exposure to escapable foot shocks, did not change cell proliferation in dentate gyrus of the hippocampus (Van der Borght et al., 2005). These data suggest that some types of stress protocols may actually increase adult hippocampal neurogenesis (Parihar et al., 2011; Van der Borght et al., 2005) and that increased survival of newly born cells in the hippocampus might also be associated with increased susceptibility to the negative effects of stress (Lagace et al., 2010).

2.1. Selectively-bred strains

Another approach to interrogate whether changes in adult hippocampal neurogenesis correlate with resilience or susceptibility to stress is to examine whether certain rodent strains or genetic mouse models that exhibit alterations in susceptibility to stress-induced changes in behaviour also display alterations in adult hippocampal neurogenesis. HAB and LAB rats and mice have been bred for high and low anxiety behaviour, respectively (Landgraf and Wigger, 2002; Sartori et al., 2011). Interestingly, prenatal stress has been reported to decrease the survival of newly-generated cells as well as neurogenesis in the hippocampus of HAB rats only (Lucassen et al., 2009), and these rats also exhibited increased social avoidance when compared with LAB rats under non-stress conditions (Henniger et al., 2000). Interestingly, HAB mice exhibit a lower rate of adult hippocampal neurogenesis along with impaired functional integration of newly-born neurons when compared with their normal anxiety/depression-related behaviour (NAB) counterparts (Sah et al., 2012). However, the ability of chronic treatment with fluoxetine to alleviate depression-like behaviour in HAB mice is dissociated from changes in adult hippocampal neurogenesis (Sah et al., 2012).

2.2. Transgenic studies

The use of knockout animals helps to determine the importance of some factors, such as brain-derived neurotrophic factor (BDNF), on the stress response. Deficiency in BDNF makes male mice susceptible to acute and subchronic mild stress (induced by intraperitoneal injection) and increases behavioural despair and plasma corticosterone levels (Advani et al., 2009), and this is coupled with reduced adult hippocampal neurogenesis (Taliaz et al., 2010). Moreover, BDNF is required for antidepressant-induced increases in the survival of newly-born neurons and antidepressant-related behaviour in mice (Sairanen et al., 2005). Thus, BDNF seems to play a role in stress susceptibility, adult hippocampal neurogenesis and antidepressant-induced changes in behaviour.

Similarly, mice lacking the cannabinoid receptor, CB1, are greatly susceptible to the anhedonic effects of chronic stress (Martin et al., 2002), and exhibit 50% lower basal cell proliferation in the subgranular zone of the dentate gyrus of the hippocampus (Jin et al., 2004), as well as depressive-like responses (Steiner et al., 2008) in basal conditions. On the other hand, mice lacking the fatty acid amide hydrolase enzyme, which results in increased availability of anandamide (which acts at CB receptors), exhibit an antidepressant-like phenotype (Bambico et al., 2010) as well as increased hippocampal cell proliferation (Aguado et al., 2005). Taken together, it is clear that genetic background is an important determinant of stress-induced changes in adult hippocampal neurogenesis and stress resilience, and that certain factors that regulate adult hippocampal neurogenesis such as BDNF and cannabinoid signalling are also important determinants of stress resilience. Such factors may be important therapeutic targets for the development of drugs that promote stress resilience (Karatsoreos and McEwen, 2013; Hill and Gorzalka, 2005).

2.3. Ablation studies

Perhaps the most definitive approach to determine whether adult hippocampal neurogenesis contributes to differential stress susceptibility is to interrogate whether ablation of neurogenesis exacerbates or attenuates the physiological and behavioural responses to stress. Ablation of adult neurogenesis can be achieved by chemical (i.e. methylazoxymethanol – MAM) (Jayatissa et al., 2009; Mateus-Pinheiro et al., 2013), genetic (Schloesser et al., 2010; Snyder et al., 2011; Yu et al., 2008) and irradiation-based methods (Santarelli et al., 2003; Wu and Hen, 2014). It has been reported that a transgenic mouse model of neurogenesis inhibition exhibits a transient increase in the corticosterone response to stress as well as an attenuated dexamethasone-induced suppression of corticosterone release (Snyder et al., 2011), thus suggesting that these mice exhibit a modest overactivation of the HPA axis. On the other hand, it has been reported that ablation of adult hippocampal neurogenesis by X-ray irradiation does not impair basal HPA axis activity (Surget et al., 2011). Interestingly however, it has been reported that normalisation of HPA-axis overactivity by the antidepressant fluoxetine is dependent on intact adult hippocampal neurogenesis (Surget et al., 2011).

Most studies report that ablating neurogenesis in rodents either with X-irradiation or with methylazoxymethanol (MAM) does not increase their susceptibility to stress-induced changes in depression-related behaviour when compared with stressed neurogenesis-intact animals (Schloesser et al., 2010; Jayatissa et al., 2009; Lehmann et al., 2013; Surget et al., 2011). For example, chemical ablation of neurogenesis in rats with chronic injection of MAM did not induce anhedonia, a behaviour frequently observed following chronic stress, even though MAM reduced hippocampal cell proliferation to a similar extent as exposure to a stress protocol (Jayatissa et al., 2009). Moreover, ablating neurogenesis prevented the ability of social defeat stress to induce social avoidance behaviour, thus suggesting that inhibiting neurogenesis may promote resilience rather than susceptibility to behavioural changes induced by this particular stressor (Lagace et al., 2010). Conversely, some studies have reported that neurogenesis ablated animals show a depressive-like phenotype and increased susceptibility to stress-induced depression-like behaviour, including anhedonia and increased immobility in the forced swim test (Snyder et al., 2011; Mateus-Pinheiro et al., 2013). Taken together, the precise role of adult hippocampal neurogenesis in stress susceptibility

remains unclear as a lack of association as well as associations with both increased susceptibility and increased resilience being reported.

2.4. Environment and glucocorticoids

On the other hand, it appears that adult hippocampal neurogenesis is required for the ability of environmental factors such as environmental enrichment and physical exercise to promote stress resilience (Schloesser et al., 2010). Specifically, it was recently demonstrated that adult hippocampal neurogenesis is required for the beneficial effects of an enriched environment on antidepressant-like behaviours and recovery from stress-induced changes in behaviour (Schloesser et al., 2010). Stressed animals, when housed in an enriched environment, are rescued of the typical submissive behaviour induced by psychosocial stress, while animals housed in impoverished environment present a susceptible behaviour (Schloesser et al., 2010). The resilience to stress promoted by environmental enrichment is correlated with increased survival of newly-born cells (Schloesser et al., 2010; Tanti et al., 2012), and neurogenesis in the adult hippocampus (Tanti et al., 2012). Neurogenesis-ablated animals, even when in an environmental enrichment, presented a submissive behaviour (Schloesser et al., 2010), thus confirming the importance of adult hippocampal neurogenesis in response to stress and resilience to it. Housing animals in an enriched environment, including voluntary exercise, increases glucocorticoid levels (Stranahan et al., 2008; Vivinetto et al., 2013; Zhang et al., 2013), leading to the suggestion that this increase is essential for increased adult hippocampal neurogenesis and stress resilience (Schloesser et al., 2010; Sampedro-Piquero et al., 2014). In fact, when rats are adrenalectomized, environmental enrichment-induced increases in adult hippocampal neurogenesis are no longer apparent (Lehmann et al., 2013), thus demonstrating the requirement of glucocorticoid action on facilitating adult hippocampal neurogenesis. On the other hand, the blunted glucocorticoid action in adrenalectomized animals with intact neurogenesis generates a resilient animal, increasing cell survival (Lehmann et al., 2013). This protective effect of adrenalectomy during stress is neurogenesis-dependent (Lehmann et al., 2013). Similarly, it has been reported that moderate increases in corticosterone by some protocols of chronic stress increases adult hippocampal neurogenesis and promotes antidepressant-like behaviour (Parihar et al., 2011). Taken together, it appears that glucocorticoids, the key substrates of the stress response, play dual roles in adult hippocampal neurogenesis, reducing or increasing it depending upon the amount released and the environmental challenge and in parallel also play dual roles in both susceptibility and resilience to stress-induced changes in behaviour whereby both environmental enrichment and adrenalectomy can lead to stress-resilience.

Taken together, the precise role of adult hippocampal neurogenesis in stress susceptibility remains unclear as a lack of association as well as associations with both increased susceptibility and increased resilience have been reported. Discrepancies in the literature might be due to differences in the methodology used, such as species, type of stressor and method of ablation of neurogenesis. On the other hand, the presence of intact adult hippocampal neurogenesis has been shown to contribute to the protective effects of adrenalectomy and environmental enrichment against stress-induced changes in behaviour. Moreover, the use of genetic models supports the study of how some factors such as BDNF and cannabinoid signalling may influence adult hippocampal neurogenesis and stress susceptibility and these factors may be a future target for the treatment of stress-induced reductions in adult hippocampal neurogenesis and maladaptive behavioural responses. Fig. 1 is a schematic representation of the factors that influence adult hippocampal neurogenesis, which in turn may affect stress-resilience/susceptibility through behavioural coping strategies. Since chronic treatment with antidepressant drugs can reverse stress-induced changes and behaviour and increase adult hippocampal neurogenesis, we continue with a discussion as to whether adult hippocampal neurogenesis can predict antidepressant-induced recovery from stress-induced changes in behaviour.

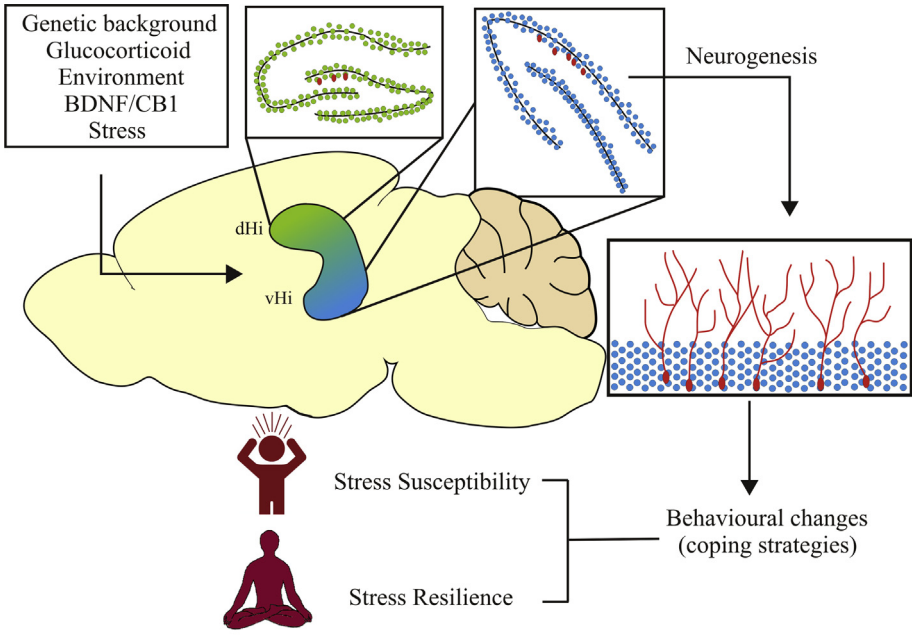

Fig. 1. Schematic view of the factors that can influence hippocampal neurogenesis, particularly on the ventral hippocampus (vHi). These neurogenic changes may modulate behavioural and neuroendocrine outputs, which can influence stress-susceptibility and stress-resilience. Newly-born neurons are represented in the figure by red cells, neurons of the dorsal hippocampus (dHi) by green cells and neurons of the ventral hippocampus (vHi) by blue cells. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3. Does adult hippocampal neurogenesis predict antidepressant-induced recovery from stress-induced changes in behaviour?

While many studies have demonstrated that antidepressant treatments increase adult hippocampal neurogenesis (Malberg et al., 2000; Jayatissa et al., 2006; Santarelli et al., 2003), surprisingly few studies have examined whether antidepressant-induced alterations in neurogenesis can predict whether an individual animal shows behavioural recovery from stress following antidepressant treatment or remains treatment-resistant to the effects of stress. Ablation of adult hippocampal neurogenesis can prevent the ability of some but not all antidepressants to reverse behavioural changes in response to stress (Surget et al., 2011; Perera et al., 2011; Santarelli et al., 2003), thus suggesting that adult hippocampal neurogenesis can contribute to antidepressant-induced recovery from stress. However, it is also important to note that negative findings have also been reported (Surget et al., 2011; Bessa et al., 2009; David et al., 2009).

In parallel, while many studies have demonstrated that chronic treatment with classic monoaminergic antidepressants can reverse stress-induced changes in depressive-like behaviour (Jayatissa et al., 2006; Bergstrom et al., 2007; Sanchez et al., 2003), it is also becoming clear that not all animals within the antidepressant-treated group exhibit behavioural recovery from stress, and thus can be stratified into responders or non-responders (Jayatissa et al., 2006; Christensen et al., 2011). This stratification of animals in responders and non-responders provides a useful approach to modelling treatment-resistant depression (Christensen et al., 2011; O'Leary and Cryan, 2013), and can be used to identify the molecular mechanisms that determine successful antidepressant response. Identifying these molecular mechanisms is key towards the development of new and more effective antidepressants (Russo et al., 2012; Hughes, 2012; O'Leary et al., in press).

Although it is clear that adult hippocampal neurogenesis is important for some of the behavioural effects of at least some antidepressants, few studies have investigated whether the rate of neurogenesis in an individual animal directly correlates with its antidepressant-induced behavioural recovery from stress. Nevertheless, it has been reported that the number of newly-born cells in the hippocampus of stressed rats was restored only in the group of rats that showed a behavioural response to the antidepressant escitalopram, thus suggesting that the restoration of cell proliferation rates at least within a certain area of the dentate gyrus (ventral region) may be important for escitalopram-induced recovery from stress-related behaviours (Jayatissa et al., 2006). Similarly, a primate study showed that fluoxetine treatment prevented the onset of depression-like behaviours and increased the number of newly-born neurons that were at the threshold of maturation within a specific region of the dentate gyrus (anterior region), thus leading to the suggestion that adult hippocampal neurogenesis may contribute to the recovery promoted by fluoxetine (Perera et al., 2011).

On the other hand the antidepressant-like effects of non-monoaminergic based antidepressant-like drugs, such as CRH1 or V1b antagonists, are not affected by inhibition of adult hippocampal neurogenesis (Surget et al., 2011; Bessa et al., 2009) which is in contrast to many findings with antidepressants that target the monoaminergic system such as fluoxetine and imipramine (Surget et al., 2011; Perera et al., 2011; Santarelli et al., 2003). Thus, it has been suggested that antidepressant drugs increase adult hippocampal neurogenesis, independently of their behavioural effects and that antidepressant-induced increases in adult hippocampal neurogenesis might not be the final process in the recovery from stress-induced depressive-like behaviour (Bessa et al., 2009).

4. A ventral view of adult hippocampal neurogenesis, stress resilience and antidepressant-induced recovery from stress

The hippocampus can be divided along its septotemporal axis into dorsal and ventral regions in rodents and into anterior and posterior regions in primates, based on their distinct afferent and efferent connections (Fanselow and Dong, 2010). Lesion, optogenetic and electrophysiological studies in rodents suggest that this anatomical segregation results in a dichotomy in the function of the dorsal hippocampus (dHi) and the ventral hippocampus (vHi) (Fanselow and Dong, 2010; Bannerman et al., 2004). While the dHi (analogous to the posterior hippocampus in primates) seems to play a preferential role in spatial learning and memory processes, the vHi (analogous to the anterior hippocampus in primates) preferentially regulates anxiety and the response to stress (Fanselow and Dong, 2010; Bannerman et al., 2004; Moser and Moser, 1998). Since adult hippocampal neurogenesis has been implicated in processes preferentially regulated by the dHi (spatial learning and memory) and the vHi (stress response), it is possible that adult neurogenesis might be regulated preferentially in the dHi or the vHi, depending upon the stimulus (Tanti and Belzung, 2013; O'Leary and Cryan, 2014). Indeed, several studies have reported that stress affects several stages of adult neurogenesis, preferentially in the vHi rather than the dHi (Tanti and Belzung, 2013; O'Leary and Cryan, 2014). Some (but not all) studies also report that antidepressant-induced increases in cytogenesis and neurogenesis occur preferentially in the vHi but not dHi (Tanti et al., 2012; Jayatissa et al., 2006; O'Leary et al., 2012; O'Leary and Cryan, 2014; Banasr et al., 2006). Together, these data suggest that adult hippocampal neurogenesis specifically in the vHi may be an important determinant of the behavioural responses to stress and antidepressant drugs.

To date however, few studies have investigated whether adult neurogenesis specifically in the vHi correlates with stress resilience or the antidepressant response. Nevertheless, in non-human primates, the number of immature neurons that were at the threshold of complete maturation was reduced by chronic stress in the anterior but not posterior hippocampus, and this effect was correlated with stress-induced anhedonia (Perera et al., 2011). Our laboratory recently reported that $GABA_{B(1b)}^{-/-}$ mice, which are resilient to stress-induced anhedonia, exhibit increased proliferation and survival of newly-born cells predominantly in the vHi, and are also resilient to stress-induced decrease in the survival of newly-born cells in the vHi (O'Leary et al., 2014b). Furthermore, Jayatissa and colleagues reported that rats that exhibit escitalopram-induced behavioural recovery from stress also exhibit increased hippocampal cell proliferation in the vHi, while this selective effect in the vHi was not observed in rats that failed to respond to escitalopram treatment (Jayatissa et al., 2006). Moreover, it was recently demonstrated that ablation of neurogenesis in the vHi but not dHi prevents the anxiolytic effects of fluoxetine in animals that had received daily foot shocks for three weeks (Wu and Hen, 2014). Future studies investigating whether the effects of fluoxetine and other antidepressants on recovery from stress-induced changes in behaviour, such as anhedonia, are dependent on neurogenesis in specifically the vHi will be of interest.

Ultimately, adult hippocampal neurogenesis may be a key factor linking stress to anxiety- and depression-like behaviours (Snyder et al., 2011). However, as discussed earlier, studies have shown contradictory results linking stress susceptibility and adult hippocampal neurogenesis. In addition to methodological differences, we suggest that such incongruences might also be due to the absence of segregation of the hippocampus into dorsal and ventral regions (O'Leary and Cryan, 2014). Therefore, future studies investigating the relationships between adult hippocampal neurogenesis and

stress-related factors such as stress susceptibility/resilience and the antidepressant response should specify whether changes in adult hippocampal neurogenesis occur in the dHi or vHi.

5. Concluding remarks

Exposure of animals to different protocols of stress has been shown to reduce adult hippocampal neurogenesis. Conversely, some protocols of stress, such as predictable stress, increase adult hippocampal neurogenesis and lead to stress resilience. Most studies show that neurogenesis-ablated animals do not show a depressive phenotype, but when exposed to stress, they can present enhanced responsiveness and stress-susceptibility, suggesting that adult hippocampal neurogenesis is important in the stress response and may be linked to stress-resilience.

Monoaminergic antidepressants and other treatments, such as environmental enrichment and adrenalectomy, have been shown to be beneficial for reversing stress-induced changes in behaviour in a neurogenesis-dependant manner. Conversely, some other antidepressants do not affect adult hippocampal neurogenesis, suggesting that adult hippocampal neurogenesis may be an intermediate process and might not necessarily be the final process governing antidepressant-induced behavioural recovery from stress. However, it is also important to note that chronic stress and some antidepressant treatments exert their effects on adult neurogenesis, specifically in the vHi, the area of the hippocampus which plays a primary role in the stress response and emotionality, and a recent study demonstrated that the anxiolytic effects of fluoxetine are dependent upon neurogenesis in this brain area (Wu and Hen, 2014). Thus, alterations in adult hippocampal neurogenesis specifically in the vHi rather than the dHi might also play a key role in recovery from stress-related disorders (Tanti et al., 2012; O'Leary and Cryan, 2014).

Given that adult hippocampal neurogenesis is implicated in a host of fundamental emotional and cognitive processes, ranging from pattern separation (Sahay et al., 2011; Clelland et al., 2009) to forgetting (Frankland et al., 2013), it will be important to identify and understand the mechanism of how newly-born neurons specifically contribute not only to the response and recovery from stress, but also to distinct cognitive functions, some of which might also be disrupted in stress-related psychiatric disorders (Kheirbek et al., 2012). This may guide future approaches for the treatment of psychiatric disorders.

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