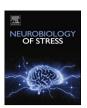
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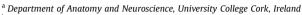
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Role of adult hippocampal neurogenesis in stress resilience

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ARTICLE INFO

Article history:
Received 20 August 2014
Received in revised form
30 October 2014
Accepted 3 November 2014
Available online 21 November 2014

Keywords: Stress Resilience Susceptibility Vulnerability Hippocampus Neurogenesis

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 stressrelated psychiatric disorders.

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1. Introduction

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

Hans Selve

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

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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

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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 mineral corticoid 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.,

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