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Neurogenesis-independent antidepressant-like effects of enriched environment is dependent on adiponectin

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Summary Environmental enrichment (EE) that combines voluntary physical exercise, sensory and social stimuli, causes profound changes in rodent brain at molecular, anatomical and behavioral levels. Here, we show that EE efficiently reduces anxiety and depression-like behaviors in a mouse model of depression induced by long-term administration of corticosterone. Mechanisms underlying EE-related beneficial effects remain largely unexplored; however, our results point toward adiponectin, an adipocyte-secreted protein, as a main contributor. Indeed, adiponectin-deficient (adipo$^{-/-}$) mice did not benefit from all the EE-induced anxiolytic and antidepressant-like effects as evidenced by their differential responses in a series of behavioral tests. Conversely, a single intravenous injection of exogenous adiponectin restored the sensitivity of adipo$^{-/-}$ mice to EE-induced behavioral benefits. Interestingly, adiponectin depletion did not prevent the hippocampal neurogenesis induced by EE. Therefore, antidepressant properties of adiponectin are likely to be related to changes in signaling in the hypothalamus rather than through hippocampal-neurogenesis mechanisms. Additionally, EE did not modify the plasma levels of adiponectin but may favor the passage of adiponectin from the blood to the cerebrospinal fluid. Our findings provide advances in the understanding of the anxiolytic and antidepressant-like effects of EE and highlight adiponectin as a pivotal mediator.

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[1] In memoriam to our friend and colleague.

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1. Introduction

In humans, psychologically stressful situations are major risk factors for appearance of anxiety and depression symptoms. Effective treatments mainly based on monoaminergic system regulation such as tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs) are available; however, about 40% of patients with depressive disorders are partially or completely resistant to treatments. Thus, identification of novel therapeutic targets is urgently needed.

Besides antidepressant drugs, other types of therapies for depression are frequently enforced including cognitive-behavioral therapies, dietary supplements and physical exercise. By themselves or in association with the usual medication, they can improve mood in people with mild to moderate depression and prevent relapse (Babyak et al., 2000). Little is known about the molecular basis underlying such beneficial effects. In animals, accumulating evidence indicates that environmental enrichment (EE) can mimic positive life experiences in humans. The EE model typically consists of housing rodents in enlarged groups in relatively spacious cages with a variety of objects frequently changed (e.g. running wheels, houses, tunnels, nesting material etc). EE causes an increase in hippocampal neurogenesis (Kempermann et al., 1997) and enhances learning and memory and neural plasticity (Hosseiny et al., 2014; Sale et al., 2009). EE also modulates the activity of the hypothalamo-pituitary-adrenal (HPA) axis through changes in neural circuitry in the hypothalamus (Cao et al., 2010). Recent studies demonstrated that EE reverses emotional disturbances in rodent models of neurological and psychiatric disorders including schizophrenia, depression and post-traumatic stress disorders (Takuma et al., 2011). Together, EE constitutes a suitable and relevant experimental model to decipher molecular events leading to specific and desirable changes and ultimately to the improvement of cerebral functions.

In rodents, EE has positive effects through alteration of numerous hormones and neurotransmitters including factors secreted by the adipose tissue, the adipokines (Cao et al., 2010). The most abundant adipokine, adiponectin, is released into the blood stream as full-length trimers, hexamers, high molecular weight (HMW) multimers and a globular fraction called globular adiponectin (Ouchi et al., 2003). It is primarily involved in inflammatory responses, energy expenditure and glucose and lipid homeostasis (Berg et al., 2002). Interestingly, adiponectin may have more widespread influence and functionality in the brain than previously thought (Arnoldussen et al., 2014). Indeed, the major isoforms of adiponectin receptors, adipoR1 and adipoR2, are expressed throughout the brain mainly in the hypothalamus, hippocampus and cortex (Kubota et al., 2007; Liu et al., 2012). Central actions of adiponectin have been reported including increase of oxygen consumption, thermogenesis (Qi et al., 2004) and regulation of food intake (Kubota et al., 2007). More recently, antidepressant-like properties have been ascribed to adiponectin likely through neurogenesis-dependent pathways (Liu et al., 2012; Yau et al., 2014).

Glucocorticoids are the most commonly prescribed anti-inflammatory/immunosuppressant medications worldwide; however, severe neuropsychiatric disorders including depression, suicide attempt, psychosis and panic disorder have been reported in association with glucocorticoid use (Judd et al., 2014). Hypercortisolism due to the unregulated activation of the hypothalamo-pituitary-adrenal (HPA) axis is thought to be involved in anxiety/depressive symptoms in humans. A wealth of information supports stress as a causal factor of depression, largely involving chronic stress-related HPA dysregulation and toxicity from excessive glucocorticoid release (Lupien et al., 2009). Other theories posit that a down regulation of hippocampal neurogenesis underlies the disorder (Kempermann and Kronenberg, 2003). David and coll. have established a relevant model of anxiety/depressive-like state that mimics HPA dysfunction (David et al., 2009); it consisted in a continuous input of glucocorticoid (corticosterone) in the drinking water of mice for several weeks. In this model, the abolishment of hippocampal neurogenesis blocked the efficacy of the antidepressant fluoxetine in some, but not all, behavioral paradigms, indicating that antidepressants may act through both neurogenesis-dependent and -independent mechanisms (David et al., 2009).

Here, we investigate the possible beneficial effects of EE on depression- and anxiety-relevant behaviors using the mouse model described above. We show that EE efficiently reverses anxiety/depressive-like state induced by long-term exposure to corticosterone as evaluated using a panel of behavioral tests (i.e. open-field (OF), light and dark (L&D), forced swim test (FST), novelty suppressed feeding (NSF) and learned helplessness (LH) tests). Our results point toward adiponectin as a main mediator of the ''positive stress'' since adiponectin depletion results in a partial insensitivity to beneficial effects of EE likely through neurogenesis-independent mechanisms. Antidepressant properties of adiponectin may be linked to changes in signaling in brain areas other than the hippocampus, as neuronal activation was detected only in the hypothalamus after intravenous (i.v.) injection of exogenous adiponectin.

2. Materials and methods

2.1. Materials

Globular adiponectin and corticosterone immunoassay were purchased from Enzo Life Sciences, BrdU, paraformaldehyde, corticosterone and β-cyclodextrine from Sigma.

2.2. Mice

Four week-old male wt or adiponectin knockout (adipo$^{-/-}$) mice with the same C57BL/6J genetic background were randomly assigned into different treatment groups and housed at 22 °C with a 12-h light-dark cycle (lights on at 07:00) with free access to beverage and chow (A04, SAFE). Mice housed either in standard ''SE'' (six/cage of $32L \times 17W \times 15H$ cm i.e. 91 cm^2/mouse) or enriched environment ''EE'' (twelve/cage of $57L \times 40W \times 20H$ cm i.e. 190 cm^2/mouse) received corticosterone (35 mg/l dissolved in tap water containing 4 g/l β-cyclodextrine) *ad libitum* or vehicle alone for six consecutive weeks. While the SE cages