Environmental influence on biomarkers of depression and anxiety in the hippocampus in an animal model of depression

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Abstract

Animal models have been used extensively to investigate depression and anxiety. In humans, anxiety and depression are typically twice as prevalent in women versus men; however the large majority of studies using animal models are based on male rats. This study addresses this issue by studying two strains of female rodents. As a continuation of a previous study on the influence of environmental manipulation in depressive-like behaviour, this study examines the difference in biomarkers related to depression and anxiety in the brains of an animal model selectively bred for depressive-like symptoms, the Wistar Kyoto rat, and its control counterpart, the Wistar rat. Before sacrifice, the animals were housed in three different environments for four weeks: standard (three animals per cage with no physical enrichment), enriched (six animals with physical enrichment) and isolated (one animal per cage without physical enrichment). Biomarkers for glucocorticoid receptors, microglia and astroglia were investigated in the hippocampus. High flown stress levels, resulting from depression and anxiety, are believed to double the function of the HPA axis altering the concentration of glucocorticoid receptors. The brains of the tested rodents were isolated and 16m coronal slices were used for immunohistochemical analysis. Immunohistochemistry was used to label the biomarkers of interest using antibodies and fluorescence microscopy was used to image the brain tissue. More work is still necessary to determine the influence of environment on the treatment of depression and anxiety. Further animal studies may lead to increased knowledge for clinical application in humans.

Introduction

Depression and Anxiety

Depression and anxiety are debilitating and prevalent mental disorders, making them the topic of many animal studies. Depression and anxiety have high rates of co-occurrence, suggesting related biological mechanisms (Barlow et al 2015).

Biological Background

It has been suggested that both depression and anxiety are result of an overactive neurobiological response to stressful life events or chronic stress (Barlow et al 2015). The Hypothalamic-pituitary-adrenal (HPA) axis regulates secretion of cortisol. Cortisol (a glucocorticoid) is a hormone released from the adrenal cortex in response to stress and is responsible for mounting the physiological stress response (i.e. increased heart rate, fight of flight response). The HPA axis has many feedback inputs to regulate the amount of circulating cortisol. One such feedback loop involves the hippocampus. Cortisol binds to glucocorticoid receptors in the hippocampus, which sends signals back to the HPA axis to stop production of more cortisol (negative feedback regulation) (Bear et al 2007). In other words, a dysregulation in the number of glucocorticoid receptors in the hippocampus can directly affect the amount of circulating cortisol, and has been implicated in biological models of anxiety and depression.

Environmental Influence

Studies suggest an integrative role of biological vulnerability and environmental influences on the development of depression and anxiety (Barlow et al 2015). Social support and physical activity can have a positive influence on mild to moderate depression. This study aims to see if they will also help in an animal model of ‘clinical’ depression at the biological level. We are also trying to see what kind of biological influence environmental enrichment or impoverishment can have.

Main Question

Can environmental manipulation influence the concentration of biomarkers of depression and anxiety in the hippocampus in an animal model of depression?

Methodology

Subjects:

• Wistar rats → control
• Wistar Kyoto rats → animal model of depression
• All female rats were used in this study

Environments:

• Standard environment → three animals per cage without physical enrichment
• Enriched environment → six animals per cage with physical enrichment
• Isolated environment → one animal per cage without physical enrichment

Following behavioural studies:

• Subjects were sacrificed
• Brains were isolated, perfused and flash frozen
• Brains were sectioned into 16m coronal slices
• Slices containing hippocampal regions were then used for immunohistochemical analysis

Immunohistochemistry:

• Application of primary antibodies
  • GR → glucocorticoid receptors
  • GFAP → astroglia
• Application of secondary antibodies
  • GR → fluoroses green
  • GFAP → fluoroses red
• Application of Hoechst
  • Labels cell nuclei
• Imaging by Fluorescence microscope

Fluorescence Images

Regions of Interest:

• CA1
• DG
• CA3

References


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