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Research Report

Differences in the brain expression of c-fos mRNA after restraint stress in Lewis compared to Sprague–Dawley rats

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ABSTRACT

In order to study the contribution of genetic factors to the pattern of stress-induced brain activation, we studied the expression of c-fos mRNA, a marker of neuronal activity, in male Sprague–Dawley and Lewis strains, the latter being known to have a deficient responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis. Immobilization (IMO) alone or combined with the immersion into water at 21 °C was applied for 15 or 60 min. The expression of c-fos mRNA was quantified by in situ hybridization in those brain areas that represent important parts of neuronal circuits activated by stress: medial prefrontal cortex, medial amygdala, lateral septum ventral part, paraventricular nucleus of the hypothalamus and locus coeruleus. While in controls, c-fos mRNA was not detectable in tested brain areas, both types of stressors induced a strong expression of this immediate early gene. There were only small differences in c-fos mRNA expression related to the type of stressor or the length of exposure to them. However, there were remarkable differences in the expression between the two rat strains. When compared to Sprague–Dawley rats, Lewis rats showed a reduced c-fos mRNA expression after both stressors in most brain areas, which may be related to the reduced responsiveness of HPA axis and also with other abnormal responses in this strain. However, this hyporesponsiveness was not observed in all brain areas studied, suggesting that there is not a generalized defective c-fos response to stress in Lewis rats and that some responses to stress may be normal in this strain.

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Abbreviations:
ACTH, adrenocorticotropic hormone
AMPH, amphetamine
ANOVA, analysis of variance
AVP, arginine vasopressin
BST, bed nucleus of stria terminalis
CO, control animals
CRF, corticotrophin-releasing factor
EDTA, ethylenediaminetetraacetic acid
DEPC, diethylpyrocarbonate
DTT, dithiothreitol
HPA, hypothalamic–pituitary–adrenal axis
IL, infralimbic area
IL 1-β, interleukin 1-β
IMO, restraint (immobilization) stress
IMO + C, restraint stress combined with immersion of rats in water
LSv, lateral septum ventral part
LE, Lewis rats
LC, locus coeruleus
M1, motor M1 area of the cortex
MeA, medial amygdala
MePOA, medial preoptic area
PFA, paraformaldehyde
KPBS, potassium phosphate buffered saline
mPFC, medial prefrontal cortex
PrL, prelimbic area
PVN, paraventricular nucleus
SSC, saline sodium citrate
SD, Sprague–Dawley rats
SMA, sympatho–medullo–adrenal axis
TEA, triethanolamine

1. Introduction

There is an ample evidence for genetic differences in behavioral and physiological responsiveness to stressors in both rats and mice; most of them were obtained in the studies of selected inbred strains. In the rat, special attention has been paid to Lewis (LE) rats; these animals, particularly when compared with the histocompatible Fischer 344 strain, were shown to be prone to develop autoimmune diseases such as arthritis (Sternberg et al., 1989a), and are characterized by a defective adrenocortical responsiveness to both emotional and immunological stressors (Armario et al., 1995; Armario and Marti, 1996; Dhabhar et al., 1993; Grota et al., 1997; Sternberg et al., 1989a). This defective adrenocortical response after immune stressors explains, in great part, the susceptibility of LE rats to autoimmune diseases; it may be caused by a lower negative feedback action of glucocorticoids on immune activation as compared to other strains (Sternberg et al., 1989b).

When LE rats have been simultaneously compared to several rat strains, they always showed the lowest ACTH and corticosterone responses to stressors (Armario and Marti, 1996; Armario et al., 1995), suggesting that the defect is not mainly located at the adrenal level. The mechanisms underlying this defective ACTH and corticosterone response are not fully understood, but they likely involve (a) a defect at the level of CRF synthesis and secretion in the paraventricular nucleus of the hypothalamus (Sternberg et al., 1989b, 1992; Zelazowski et al., 1993), (b) a reduced responsiveness of the corticotropes to CRF (Sternberg et al., 1989b; Zelazowski et al., 1992) and (c) a reduced adrenocortical response to circulating ACTH (Grota et al., 1997).

Whether the hyporesponsiveness of LE rats is restricted to the HPA axis or whether these rats are characterized by a generalized lower responsiveness to stressors has not been extensively studied. Whereas a defective hyperglycemic response to stress has been reported in LE rats (Armario et al., 1995), their prolactin response appears to be normal (Armario et al., 1995; Klenerova et al., 2001; Michaud et al., 2003). Considering that stress-induced hyperglycemia is strongly related to stress-induced adrenaline release, it appears that Lewis rats may be characterized by defective