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Research Report

Chronic corticosterone decreases brain-derived neurotrophic factor (BDNF) mRNA and protein in the hippocampus, but not in the frontal cortex, of the rat

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Abbreviations:
5-HIAA, 5-hydroxyindoleacetic acid
5-HT, 5-hydroxytryptamine
BDNF, brain-derived neurotrophic factor
ELISA, enzyme-linked immunosorbent assay
MR, mineralocorticoid receptor

ABSTRACT

This study examined the effects of chronic corticosterone (32 mg/kg/day, s.c., 21 days) on brain-derived neurotrophic factor (BDNF) mRNA and protein in the frontal cortex and hippocampus of the rat. Because evidence suggests that BDNF is an important determinant of the function of the 5-hydroxytryptamine (5-HT) system, we also quantified tissue levels of 5-HT and its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA), to investigate if changes in BDNF mRNA and protein paralleled changes in the 5-HT system. Corticosterone modestly decreased BDNF protein (−16.6%) in whole hippocampus and BDNF mRNA (−19%) in the CA3 area. In contrast, BDNF mRNA and protein in the frontal cortex were unchanged. In both the frontal cortex and hippocampus, tissue levels of 5-HT and 5-HIAA were increased and decreased, respectively. Combined, these data suggests that the effects of corticosterone on the BDNF system are not linked to the effects on the 5-HT systems. However, our findings do suggest that chronic corticosterone impairs hippocampal BDNF function, a finding with potential relevance for the hippocampal atrophy reported in major depression. Additionally, as inferred from the alterations in tissue levels of 5-HT and 5-HIAA, chronic corticosterone may influence the function of the 5-HT system.

1. Introduction

Over the last decade the *brain-derived neurotrophic factor* (BDNF) hypothesis of depression and antidepressant action has been highly influential (Manji et al., 2003). BDNF administration was reported to display antidepressant-like activity in rodent models of depression and to support the function of the 5-hydroxytryptamine (5-HT) system (Lyons et al., 1999; Siuciak et al., 1996, 1997). Further, increased BDNF mRNA expression in the hippocampus was reported to be a shared action of different antidepressant treatments (Nibuya et al., 1995), although later studies have not always replicated these finding (Jacobsen and Mork, 2004; Miro et al., 2002). Conversely, acute or 7 days immobilization stress decreased BDNF mRNA expression in the hippocampus, partly via a corticosterone-dependent mechanism (Smith et al., 1995). In adrenalecto-

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mized rats, acute administration of exogenous corticosterone decreased hippocampal BDNF mRNA expression 3 h after injection while an increase was noted at 12 h. In the same study, hippocampal BDNF *protein* levels were decreased at 4 and 6 h after corticosterone, but later time points were not examined (Schaaf et al., 1998). However, adrenalectomy *per se* enhances hippocampal BDNF mRNA expression (Chao et al., 1998) and effects of corticosterone may differ between adrenal-intact and adrenalectomized rats. In fact, 7 days corticosterone did not significantly alter BDNF mRNA expression in the hippocampus of adrenal-intact rats (Chao and McEwen, 1994). Thus, although the extent of the interaction is unsettled, a possible link between corticosterone and the BDNF system is intriguing because elevated glucocorticoids may contribute to the pathology of depression in humans (de Kloet et al., 2005).

Modulations on the mRNA level does not necessarily become manifest on the protein level. For instance, it was reported that antidepressants modulate G-proteins and their coding mRNA's dissimilarly (Lesch and Manji, 1992). In a previous study, we therefore performed parallel measurement of BDNF mRNA and protein in the frontal cortex and hippocampus and found that BDNF mRNA and protein were modulated dissimilarly by chronic antidepressant treatments (Jacobsen and Mork, 2004). Anterograde axonal transport of BDNF protein could account for the BDNF mRNA/protein discrepancy in the frontal cortex, though likely not in the hippocampus where BDNF is synthesized predominantly in neuronal populations projecting internally in the hippocampus (Altar et al., 1997; Conner et al., 1997). Thus, treatment-induced changes in BDNF mRNA expression may not always be reflected on the BDNF protein level. Dual protein/mRNA measurements may provide a better assessment of the effect of a given manipulation on the BDNF system.

In the present report, we investigated the effect of 21 days treatment with corticosterone on BDNF mRNA and protein in the frontal cortex and hippocampus of the rat. Dysfunction of these regions has been reported in depression in humans (Kennedy et al., 1997; Sheline et al., 1996). Further, BDNF may provide important trophic support for the 5-HT system (Lyons et al., 1999). We therefore examined if corticosterone modulations of BDNF mRNA and/or protein compared to modulations of tissue 5-HT and 5-hydroxyindoleacetic acid (5-HIAA; the main metabolite of 5-HT).

2. Results

2.1. *BDNF mRNA expression*

Chronic corticosterone treatment had no effects on BDNF mRNA in the frontal cortex and dentate gyrus of the hippocampus. In contrast, in the CA3 corticosterone decreased BDNF mRNA expression by 19% ($p<0.001$) (Figs. 1B and 2A). BDNF mRNA expression in the CA1 area of the hippocampus was very low and could not be reliably quantified (Fig. 1B).

2.2. *BDNF protein levels*

In the frontal cortex, there was no significant difference in BDNF protein levels between the corticosterone and vehicle

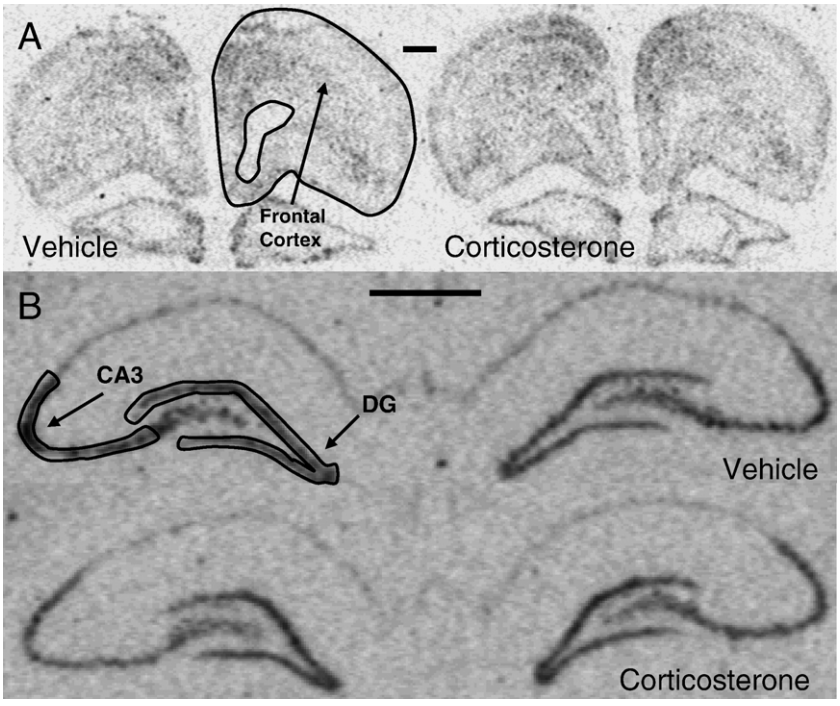

Fig. 1 – Representative autoradiographs showing BDNF mRNA expression in the frontal cortex (A) (3.2 mm relative to bregma) and hippocampus (B) (–3.3 mm relative to bregma). Areas quantified are delineated. Frontal cortices from 21 days corticosterone and vehicle treated rats (A). Note similar level of BDNF mRNA expression. Hippocampi from 21 days corticosterone- and vehicle-treated rats (B). Note the decrease in BDNF mRNA expression in the CA3, but not DG (B). Scale bars, 1 mm.