



CENTRAL BDNF LEVELS IN AN ANIMAL MODEL OF DEPRESSION

S. R. Hauser¹, B. Getachew¹, R. Das¹, K. Manaye², L. Russell¹, and Y. Tizabi¹
 Departments of ¹Pharmacology, ²Physiology and Biophysics, College of Medicine
 Howard University, Washington, DC 20059



INTRODUCTION

Recent findings strongly suggest that the brain-derived neurotrophic factor (BDNF) may play an important role in pathogenesis of depression and the response to antidepressants. Indeed, it has been suggested that increases in hippocampal BDNF activity may be both necessary and sufficient for any antidepressant activity. Wistar Kyoto (WKY) rats, derived from Wistar (WIS) stock are considered a suitable animal model of depression. The aim of this study was to test the hypothesis that WKY rats would exhibit a lower concentration of BDNF in the hippocampus compared to WIS rats. Moreover, it was reasoned that treatment with an antidepressant that would ameliorate the depressive-like characteristics of the WKY rats would also normalize the BDNF levels in the hippocampus.

METHODS

Animals

Age matched adult female WKY and Wistar rats (Harlan) were kept in a temperature-controlled room (24-26°C) on a 12:12 hour reversed light/dark cycle (lights on at 19:00). The animals had *ad libitum* access to food and water, except during experiments. Adult female WIS and WKY rats were tested for their open field locomotor activity (LCA) and their performance in the forced swim test (FST). Another set of WKY rats were treated daily for ten days with the clinically effective tricyclic antidepressant imipramine (10 mg/kg, i.p) which selectively blocks serotonin (5HT) and norepinephrine (NE) uptake or with nomifensine (10 mg/kg, i.p) which is most selective for blocking NE uptake, but can also block the uptake of dopamine (DA) and were tested for the behavioral effects on the eleventh day followed by BDNF analysis.

Behavioral Testing:

Locomotor Activity Test (LCA) On the day of behavioral testing automated analysis of LCA in an open field was performed for 10 minutes prior to the forced swim test (FST).

Forced Swim Test (FST)

A modification of the method of Porsolt et al. (1977) was used. The FST measures immobility of animals in an inescapable cylinder of water. The total amount of time the animal demonstrates this behavior reflects the animal's state of behavioral despair. The animals were placed in the water cylinders for 5 minutes, videotaped and their swimming and immobility were scored at every 5 second interval according to Detke et al. (1995).

BDNF Assay in the Hippocampus, Hypothalamus and Frontal Cortex

Animals were sacrificed by decapitation. Three brain regions: hippocampus, hypothalamus and frontal cortex were evaluated for the BDNF levels using ELISA kits. The discrete brain regions were placed in 1.0 ml of ice cold lysis buffer (pH 8.0) containing 137mM NaCl, 20mM Tris-HCl (pH 8.0), 1% Igepal, 10% glycerol, 1mM phenylmethylsulfonyl fluoride (PMSF), 10µg/ml aprotinin, 1µg/ml leupeptin and 0.5mM sodium vanadate. After adding buffer to the tissue, samples were homogenized and then centrifuged for 10 min at 10,000 rpm (4 °C). Promega BDNF Emax® ImmunoAssay System was used to determine the levels of BDNF which was expressed per protein content of the areas analyzed.

Statistical Analysis

One-way ANOVA followed by Tukey's post hoc was used for statistical analysis.

RESULTS

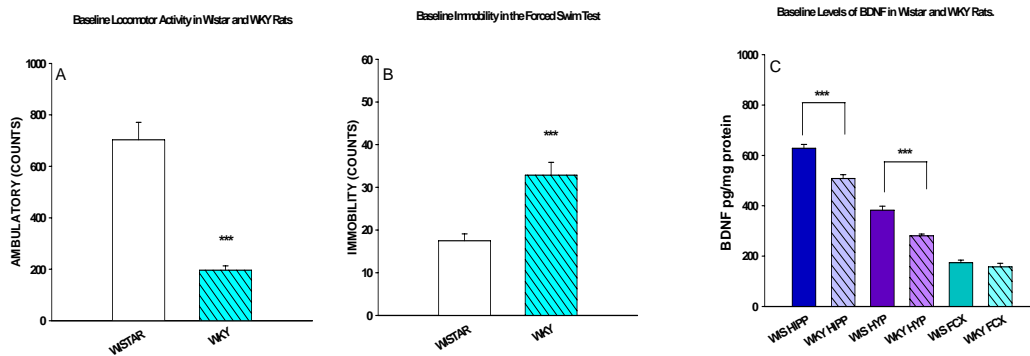


Figure 1: Locomotor Activity (A), immobility in the FST (B), and baseline BDNF levels (C) in the hippocampus, hypothalamus, and Frontal Cortex (C). Values are mean ± SEM. ***P < 0.001 Wistar vs WKY (N = 7-9).

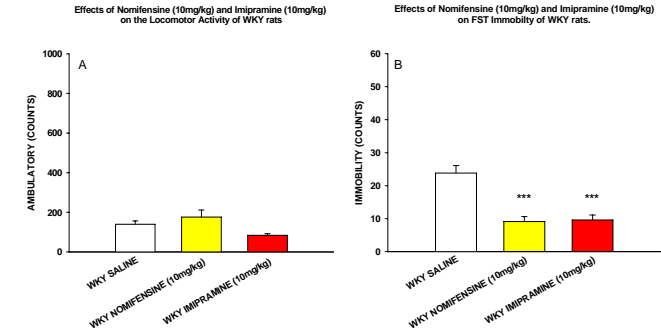


Figure 2: Locomotor activity (A) and immobility in FST (B) after 10 days of nomifensine (10mg/kg) and imipramine (10mg/kg) treatment. Values are mean ± SEM. ***P < 0.001 Tx vs saline (N = 7-9)

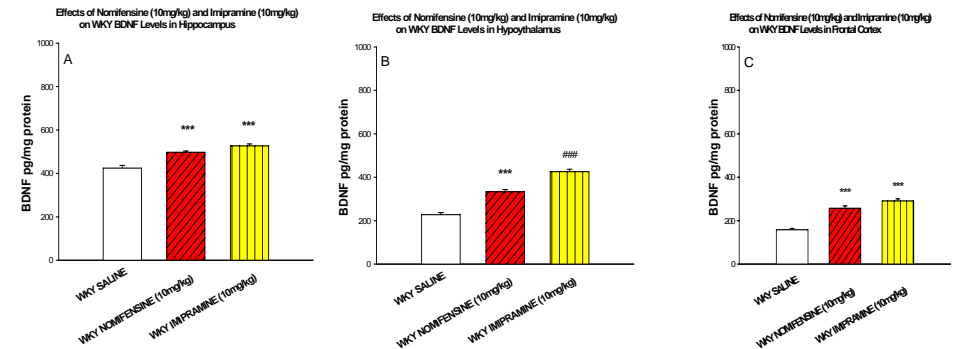


Figure 3: BDNF levels in the hippocampus (A), hypothalamus (B) and frontal cortex (C) after 10 days of nomifensine (10mg/kg) and imipramine (10mg/kg) treatment. Values are mean ± SEM. ***P < 0.001 Tx vs saline (N = 7-9) ####P < 0.0001 nomifensine vs imipramine and saline

Summary of Results

- As seen previously, WKY rats had a lower score in LCA and higher immobility in the FST, reflective of their depressive-like characteristics.
- BDNF levels in the hippocampus and the hypothalamus of WKY rats were significantly lower than in WIS rats. No significant difference in frontal cortex BDNF between the two strains was observed.
- Daily treatment with imipramine or nomifensine significantly lowered the immobility of the WKY rats in the FST and increased the BDNF level in all areas. The effect of imipramine on hypothalamic BDNF was more pronounced than that of nomifensine.

Concluding Statement

These results while suggesting a role for central BDNF in depressive-like characteristics of WKY rats further validate the use of these rats as an animal model of depression. Moreover, the findings provide additional support for a role of central BDNF in effectiveness of antidepressants.