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INDIVIDUAL DIFFERENCES IN THE FORCED SWIMMING TEST AND THE EFFECT OF ENVIRONMENTAL ENRICHMENT: SEARCHING FOR AN INTERACTION

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Abstract—Animals with low and high immobility in the forced swimming test (FST) differ in a number of neurobehavioral factors. A growing body of evidence suggests that the exposure to enriched environments mediates a number of changes in the brain. Therefore, we studied if animals' individuality can somehow modulate the response to environmental stimuli. Male rats were classified according to their immobility time scores in the FST test session as animals with low, medium or high immobility. Then, rats from groups with low and high immobility were randomly distributed in two groups to be reared in different housing conditions (i.e., enriched and standard conditions) during 8 weeks. Animals were subjected to the open field test (OFT) before and 6 weeks after the start of housing protocol. Rats with high immobility in the FST also showed high ambulation and high rearing time in the first OFT. Such findings were not observed in the second OFT. Conversely, an effect of environmental enrichment was found in the second OFT where enriched animals showed lower ambulation and higher grooming time than the standard control group. Rats were sacrificed after the housing protocol and neurochemical content and/or gene expression were studied in three different brain regions: the prefrontal cortex, the hippocampus and the nucleus accumbens. Rats with low immobility showed significantly higher accumbal 5-HT levels than animals with high immobility, whereas no neurochemical differences were observed between enriched and standard animals. Regarding expression data, however, an effect of enrichment on accumbal corticotropin-releasing factor (CRF) and its receptor 1 (CRFR1) levels was observed, and such effect depended on immobility levels. Thus, our results not only allowed us to identify a number of differences between animals with low and high immobility or animals housed in standard and enriched conditions, but also suggested that animals' individuality modulated in some way the response to environmental stimuli. **© 2014 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: individual differences, environmental enrichment, neurotransmitters, gene expression, nucleus accumbens.

INTRODUCTION

The study of behavioral individual differences, that is, classification of individuals according to systematic variations of specific behaviors, has shown to be a very useful tool in the research of brain function and mood disorders (Ho et al., 2002; Lathe, 2004; Kazlauckas et al., 2005; Görisch and Schwarting, 2006). In order to analyze individual behavior a cohort of animals is exposed to a behavioral test and, afterward, divided into at least two groups (i.e., high and low responders) according to the scores for specific behavioral responses (for a review see Pawlak et al., 2008). Given that an individual phenotype can be influenced by several interacting factors such as genetic variation, endocrine status and environmental effects (Lathe, 2004), the study of individual differences provides an important methodological approach to identify such factors and to analyze components underlying the development of mood disorders (Pawlak et al., 2008). Accordingly, several groups have used this approach to study anxiety- (Borta and Schwarting, 2005; Herrero et al., 2006; Antoniou et al., 2008) and depression-related behaviors (Taghzouti et al., 1999; Naudon and Jay, 2005; Enríquez-Castillo et al., 2008).

On the other hand, the environment exerts a significant modulator effect on brain function and, therefore, it plays a relevant role in both normal and atypical development of the central nervous system (Heim et al., 2004; Paus, 2013). Environmental enrichment has shown to be a useful approach to comprehend functional issues underlying the effects of psychosocial and physical environments (Petrosini

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Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; BDNF, brain-derived neurotrophic factor; CRF, corticotropin-releasing factor; CRFR1, CRF receptor 1; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; EDTA, ethylenediaminetetraacetic acid; FST, forced swimming test; HPC, hippocampus; HPLC, high-performance liquid chromatography; HPRT1, hypoxanthine phosphoribosyltransferase 1; NAc, nucleus accumbens; NE, noreprinephrine; OFT, open field test; PFC, prefrontal cortex; PND, postnatal day; PPIA, peptidylprolil isomerase A; TrkB, tropomyosin receptor kinase B.

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et al., 2009; Reynolds et al., 2010). Such approach involves the exposure of laboratory animals to physical and/or social stimulation that is significantly greater than that which they would receive being housed under standard conditions (Rosenzweig and Bennett, 1996). Strategies for physical enrichment take into account structural modifications such as an increase of space availability and the inclusion of elements favoring exercise, games and exploration, whereas social enrichment involves the housing of animals in groups (Stewart and Bayne, 2004).

The exposure to enriched environments mediates a number of behavioral, biochemical and structural changes (reviewed in Nithianantharajah and Hannan, 2006; Petrosini et al., 2009; Reynolds et al., 2010). Enrichment has proven to reduce levels of anxiety- and depression-related behaviors (Hellemans et al., 2005; Brenes et al., 2008), and to increase learning and memory (Larsson et al., 2002). Animals reared in enriched environments show an increase in the expression of serotonin 1A ($5\text{-}HT1_A$) receptors in the hippocampus (HPC) (Rasmuson et al., 1998), and an increase of the 5-HT levels in the HPC and the prefrontal cortex (PFC) (Brenes et al., 2008). In addition, other neurotransmitters levels such as glutamate and GABA are modulated by the effect of differential housing conditions (Segovia et al., 2006). Additionally, it has been shown that enriched environments affect the expression of the brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in several brain regions such as the HPC and the PFC (Ickes et al., 2000). In fact, studies using microarrays suggest that environmental enrichment induces short-term changes (i.e., identifiable within hours) in the expression profiles of genes involved in processes such as neural differentiation, cognition, neural excitability, the formation of new synapses, and the reorganization or strengthening of the existing ones (Rampon et al., 2000).

We have previously shown that the use of individual differences in the forced swimming test (FST) is a useful approach to identify neural factors related to stress response and depression-associated behaviors (Sequeira-Cordero et al., 2013b). Our results showed that individuals with high and low immobility in the FST may differ in the expression of the corticotropin-releasing factor receptor 1 (CRFR1) and dopaminergic neurotransmission in the nucleus accumbens (NAc). Thus, based on the above overview concerning enrichment effects on behavior and neurochemistry, we hypothesized that animals with low and high immobility in the FST would differentially respond to enriched environments. Therefore, we investigated if animals classified as individuals with low and high immobility in the FST differentially responded to the exposure to enriched or standard conditions, analyzing behavior in the open field test (OFT), the neurochemical content and/or mRNA levels of CRF, CRFR1, BDNF and its tropomyosin receptor kinase B (TrkB) in the PFC, the HPC and the NAc. Accordingly, the aim of the study was to assess a putative interaction between intrinsic individual features (i.e., individual differences) and the effect of environmental manipulations. Such brain areas and target genes were chosen taking into account their role as modulators of stress response and/or enrichment effects (see above). The existence of such interaction would point to factors associated with the development of behavioral differences that, in turn, are targeted by environment.

EXPERIMENTAL PROCEDURES

Animals

Eighty outbred male Sprague–Dawley rats (*Rattus norvegicus*) were used (provided by LEBi Laboratories, University of Costa Rica). The animals were transferred to our animal housing room at postnatal day (PND) 21, individually marked and housed in groups in separated polycarbonate home cages (8 animals/cage until they were distributed to different housing conditions), with *ad libitum* access for food and water, under a 12:12-h light–dark schedule (light on at 6:00 am until 6:00 pm), with room temperature at 25.5 °C ± 1.20 °C and 78–87% of relative humidity. A one-week habituation period was used in order to reduce the stress associated to the new environment (i.e., our housing room). Afterward, animals were subjected to the FST from PND 30 to PND 35, and rats with low and high immobility were housed in standard and enriched conditions (see below). Experimental procedures were done in accordance with the guidelines of the Costa Rican Ministry of Science and Technology for the Care and Use of Laboratory Animals and were approved by the Institutional Committee for Animal Care and Use of the University of Costa Rica.

Experimental design

All rats were subjected to the FST from PND 30 to PND 35 and classified according to their immobility time (in seconds) in the 5-min FST test session as animals with low (lower quartile) or high (upper quartile) levels of immobility resulting in 20 animals/group. Animals showing medium scores were not included in this study ($n = 40$). Animals with low and high immobility were subjected to the first OFT1 from PND 40 to PND 44. Once tested, rats from each mobility group were randomly distributed in two differentially housed groups: enriched or standard conditions (10 animals/housing condition). The housing protocol was started on PND 45 and animals were maintained in these different housing conditions (i.e., standard and enriched conditions) for 8 weeks. A second OFT (OFT2) was carried out around 6 weeks after the start of the housing protocol (ranging from 39 to 43 days, from PND 84 to PND 88) in order to obtain behavioral markers of housing effects (Brenes et al., 2009). Animals were sacrificed on PND 100. The OFT2 was carried out 2 weeks before finishing the protocol and not at the end of it in order to avoid a putative effect of the behavioral test on the expression of the target genes included in the experiment. Fig. 1

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