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Effects of 5-h multimodal stress on the molecules and pathways involved in dendritic morphology and cognitive function

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ABSTRACT

Stress induces cognitive impairments, which are likely related to the damaged dendritic morphology in the brain. Treatments for stress-induced impairments remain limited because the molecules and pathways underlying these impairments are unknown. Therefore, the aim of this study was to find the potential molecules and pathways related to damage of the dendritic morphology induced by stress. To do this, we detected gene expression, constructed a protein–protein interaction (PPI) network, and analyzed the molecular pathways in the brains of mice exposed to 5-h multimodal stress. The results showed that stress increased plasma corticosterone concentration, decreased cognitive function, damaged dendritic morphologies, and altered *APBB1*, *CLSTN1*, *KCNA4*, *NOTCH3*, *PLAU*, *RPS6KA1*, *SYP*, *TGFB1*, *KCNA1*, *NTRK3*, and *SNCA* expression in the brains of mice. Further analyses found that the abnormal expressions of *CLSTN1*, *PLAU*, *NOTCH3*, and *TGFB1* induced by stress were related to alterations in the dendritic morphology. These four genes demonstrated interactions with 55 other genes, and configured a closed PPI network. Molecular pathway analysis use the Database for Annotation, Visualization, and Integrated Discovery (DAVID), specifically the gene ontology and Kyoto Encyclopedia of Genes and Genomes (KEGG), each identified three pathways that were significantly enriched in the gene list of the PPI network, with genes belonging to the Notch and transforming growth factor-beta (TGF-B) signaling pathways being the most enriched. Our results suggest that *TGFB1*, *PLAU*, *NOTCH3*, and *CLSTN1* may be related to the alterations in dendritic morphology induced by stress, and imply that the Notch and TGF-B signaling pathways may be involved.

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1. Introduction

Stress is a non-specific systemic body reaction caused by a change in the external environment. While moderate stress is beneficial for health, excessive stress can damage the body. Numerous studies have shown that stress causes cognitive dysfunction in a variety of organisms, including humans, mice, rats, rainbow trout, zebrafish, and rhesus monkeys. Stress has been shown to damage attention (Elling et al., 2011; Ljungberg & Neely, 2007), short-term memory (Sherwood & Griffin, 1990), sporadic memory (Hygge, Boman, & Enmarker, 2003), reading comprehension abilities (Haines, Stansfeld, Job, Berglund, & Head, 2001), and odor (Jovanovic, Perski, Berglund, & Savic, 2011) and visual (Morgan, Doran, Steffian, Hazlett, & Southwick, 2006) recognition in humans, while in rodents it can damage the passive avoidance response (Bueno et al., 1994; Cheng, Wang, Chen, & Liao, 2011), recognition memory (Chen et al., 2010), working memory (Manikandan et al., 2006), and spatial memory (Chengzhi et al., 2011; Hagewoud et al., 2010). In addition, stress has been shown to impair the passive avoidance response in rainbow trout (Johansen, Sandvik, Nilsson, Bakken, & Overli, 2011) and zebrafish (Piato et al., 2011), and the passive avoidance response and spatial working memory of rhesus monkeys (Arnsten & Goldman-Rakic, 1998). Studies have

Abbreviations: DAVID, Database for Annotation, Visualization, and Integrated Discovery; ELISA, enzyme-linked immunosorbent assay; FDR, false discovery rate; GO, gene ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; NICD, Notch intracellular domain; PCR, polymerase chain reaction; PPI, protein–protein interaction; TGF-B, transforming growth factor-beta.

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shown that the underlying mechanisms of stress-induced cognitive impairments involve alterations in dendrite morphology. For example, chronic psychosocial stress induces dendritic contraction and the loss of dendritic spines in the prefrontal cortex of humans (Liston, McEwen, & Casey, 2009). In rats, chronic stress induces dendritic contraction (Huang et al., 2011; Magarinos, McEwen, Flugge, & Fuchs, 1996; Radley et al., 2004; Woolley, Gould, & McEwen, 1990), decreases in the number of dendritic branches (Magarinos et al., 1996; Radley et al., 2004; Wang et al., 2011; Woolley et al., 1990), and the loss of dendritic spines (Goldwater et al., 2009). Furthermore, in mice, acute stress decreases the number of dendritic branches (Brown, Henning, & Wellman, 2005) and spines (Chen et al., 2010). However, treatments for the impairments induced by stress remain limited.

Studies on the mechanisms of stress-induced cognitive dysfunction and dendritic morphology alterations indicate that various pathways and molecules are involved in the biological response to stress. For instance, stress results in an imbalance of the neuroendocrine–immune network by affecting the secretion of corticotropin-releasing hormone (Chen et al., 2010) and glucocorticoids (de Quervain, Roozendaal, & McGaugh, 1998). Stress is also able to induce changes in neurotransmission (Chengzhi et al., 2011), affect the plasticity of synaptic structures (Chen et al., 2010; McEwen, 2010) and their functions (Alzoubi, Srivareerat, Aleisa, & Alkadhi, 2013; Chen et al., 2010), and impair the growth of nerve cells via reducing the levels of neurotrophic factors (Kazlauckas et al., 2011) and nerve growth factors (Muto et al., 2010). Moreover, stress has been shown to induce tau hyperphosphorylation by activating cyclin-dependent kinase 5 (Cuadrado-Tejedor et al., 2011), which eventually damages the cytoskeletal structures. In the brain, stress raises the levels of 4-hydroxy-2-noneral (Nakajima, Ohsawa, Ohta, Ohno, & Mikami, 2010) and malondialdehyde (Nagata, Nakashima-Kamimura, Mikami, Ohsawa, & Ohta, 2009), but decreases the activity of glutathione reductase (Huang et al., 2011), catalase (Kumar & Singh, 2009), and superoxide dismutase (Manikandan et al., 2006), resulting in oxidative stress. These findings show that the underlying mechanisms of the stress-induced cognitive impairments and neural deterioration are diverse and involve a complex cascade of interconnected biochemical events. The exact pathways and sequences of events that lead to different pathologies continue to be a source of debate, and the relative importance of various molecules remains controversial.

In order to identify the most important molecules and pathways involved in the stress-induced alterations in dendritic morphology and cognitive function, we exposed mice to 5-h multimodal stress and assessed the following: plasma corticosterone concentration, cognitive behaviors (passive avoidance response and object recognition memory), dendritic morphologies, differentially expressed genes, and genes related to alterations in dendritic morphology following stress. Using this information, we constructed a functional annotation of the protein–protein interaction (PPI) network inferred from the molecules (genes) related to the dendritic morphology. Finally, we analyzed the most important pathways involved in the response to stress with the Database for Annotation, Visualization, and Integrated Discovery (DAVID; gene ontology [GO] and Kyoto Encyclopedia of Genes and Genomes [KEGG]).

2. Methods

The analysis procedures are depicted in Fig. 1 and involved investigating the effects of extended, multimodal stress on neuroendocrine corticosterone level, learning and memory, dendritic structure, and molecular expression.

2.1. Animals

Male BALB/c mice (18–22 g) were housed in the Beijing Institute of Pharmacology and Toxicology under a natural 12/12-h light–dark cycle, with a temperature of 25 ± 1 °C and normal relative humidity (50 ± 5%). Food and water were available *ad libitum*. All animal care and experimental procedures were performed in strict compliance with the Guidelines of the Animal Care and Use Committee of the Laboratory Animal Center of the Beijing Institute of Medical Science.

2.2. Spontaneous locomotor activity test

After the BALB/c mice were habituated for 2 min in a black Plexiglas apparatus (width × length × height: 30 × 30 × 30 cm), their motor activity was recorded via video for 10 min and analyzed with the ANY maze software (Stoelting Co., Wood Dale, IL). The total distance traveled per mouse was indicative of its spontaneous locomotor activity. Eighty-four mice whose total distance traveled followed the normal distribution were employed for the following stress and behavioral tests (Supplementary Fig. 1).

2.3. Stress paradigm

The 5-h multimodal, combined physical/psychological stress was applied as described by Chen et al. (2010), Latt, He, Tang, Slater, and Goldstein (1995) and modified into three different degrees: light, medium, and severe stress. Briefly, mice were restrained in a 50-mL tube (cat no. 430828; Corning, USA) without food and water. Six mouse-tubes were put in a cage (290 × 178 × 160 mm) that was placed on a rapid laboratory shaker (HZQ-C; Harbin Donglian Electronic Technology Development Co., Ltd., China) in a brightly lit room bathed in loud rap music for 5 h. The degree of stress was distinguished according to the light intensity, sound intensity, and rotation speed of the laboratory shaker (Table 1). The light, medium, and severe stress were bathed in bright light of 67, 200, and 600 Lux; loud noise at 83, 100, and 120 dB; and jostling at 77, 130, and 220 rpm, respectively (Table 1).

2.4. Experiment 1: the neuroendocrine phenotype-corticosterone response to different degrees of stress

At 4, 8, and 16 min after being exposed to the 5-h multimodal stress, the BALB/c mice were sacrificed for their blood, which was centrifuged for collecting plasma. The plasma concentration of corticosterone was determined by enzyme-linked immunosorbent assays (ELISAs) using a commercially available enzyme immunoassay kit (EC3001-1; ASSAYPRO, USA) according to the manufacturer's instructions. Briefly, the plasma was diluted 1:200 and 25 μL of standard/sample were added into each well of the 96-well polystyrene microplate pre-coated with a polyclonal antibody specific for corticosterone. Then, the standard or sample was competed with biotinylated corticosterone for 2 h. After the 96-well polystyrene microplate was washed, 50 μL of streptavidin–peroxidase conjugate was added to each well and incubated for 30 min at room temperature. The microplate was then washed again, and 50 μL of chromogen substrate was added per well and incubated for 20 min at room temperature. Next, we added 50 μL of stop solution to each well, and once the color changed from blue to yellow, we immediately read the absorbance on an EnSpire microplate reader (2300; PerkinElmer, USA) at a wavelength of 450 nm. The detection limit was 0.3 ng/mL. Intra- and inter-assay variations were 5.0% and 7.2%, respectively.

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