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Novel Molecular Mechanisms for the Adaptogenic Effects of Herbal Extracts on Isolated Brain Cells Using Systems Biology

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Abstract

Introduction: Adaptogens are natural compounds or plant extracts that increase adaptability and survival of organisms under stress. Adaptogens stimulate cellular and organismal defense systems by activating intracellular and extracellular signaling pathways and expression of stress-activated proteins and neuropeptides. The effects adaptogens on mediators of adaptive stress response and longevity signaling pathways have been reported, but their stress-protective mechanisms are still not fully understood.

Aim of the study: The aim of this study was to identify key molecular mechanisms of adaptogenic plants traditionally used to treat stress and aging-related disorders, i.e., Rhodiola rosea, Eleutherococcus senticosus, Withania somnifera, Rhaponticum carthamoides, and Bryonia alba.

Materials and methods: To investigate the underlying molecular mechanisms of adaptogens, we conducted RNA sequencing to profile gene expression alterations in T98G neuroglia cells upon treatment of adaptogens and analyzed the relevance of deregulated genes to adaptive stress-response signaling pathways using in silico pathway analysis software.

Results and discussion: At least 88 of the 3516 genes regulated by adaptogens were closely associated with adaptive stress response and adaptive stress-response signaling pathways (ASRSPs), including neuronal signaling related to corticotropin-releasing hormone, cAMP-mediated, protein kinase A, and CREB; pathways related to signaling involving CXCR4, melatonin, nitric oxide synthase, GP6, Gαs, MAPK, neuroinflammation, neuropathic pain, opioids, renin-angiotensin, AMPK, calcium, and synapses; and pathways associated with dendritic cell maturation and G-coupled protein receptor-mediated nutrient sensing in enteroendocrine cells. All samples tested showed significant effects on the expression of genes encoding neurohormones CRH, GNRH, UCN, G-protein-coupled and other transmembrane receptors TLR9, PRLR, CHRNE, GP1BA, PLXNA4, a ligand-dependent nuclear receptor RORA, transmembrane channels, transcription regulators FOS, FOXO6, SCX, STAT5A, ZFPM2, ZNF396, ZNF467, protein kinases MAPK10, MAPK13, MERTK, FLT1, PRKCH,

ROS1, TTN), phosphatases PTPRD, PTPRR, peptidases, metabolic enzymes, a chaperone (HSPA6), and other proteins, all of which modulate numerous life processes, playing key roles in several canonical pathways involved in defense response and regulation of homeostasis in organisms. It is for the first time we report that the molecular mechanism of actions of melatonin and plant adaptogens are alike, all adaptogens tested activated the melatonin signaling pathway by acting through two G-protein-coupled membrane receptors MT1 and MT2 and upregulation of the ligand-specific nuclear receptor RORA, which plays a role in intellectual disability, neurological disorders, retinopathy, hypertension, dyslipidemia, and cancer, which are common in aging. Furthermore, melatonin activated adaptive signaling pathways and upregulated expression of UCN, GNRH1, TLR9, GP1BA, PLXNA4, CHRM4, GPR19, VIPR2, RORA, STAT5A, ZFPM2, ZNF396, FLT1, MAPK10, MERTK, PRKCH, and TTN, which were commonly regulated by all adaptogens tested. We conclude that melatonin is an adaptation hormone playing an important role in regulation of homeostasis. Adaptogens presumably worked as eustressors ("stress-vaccines") to activate the cellular adaptive system by inducing the expression of ASRSPs, which then reciprocally protected cells from damage caused by distress. Functional investigation by interactive pathways analysis demonstrated that adaptogens activated ASRSPs associated with stress-induced and aging-related disorders such as chronic inflammation, cardiovascular health, neurodegenerative cognitive impairment, metabolic disorders, and cancer.

Conclusion: This study has elucidated the genome-wide effects of several adaptogenic herbal extracts in brain cells culture. These data highlight the consistent activation of ASRSPs by adaptogens in T98G neuroglia cells. The extracts affected many genes playing key roles in modulation of adaptive homeostasis, indicating their ability to modify gene expression to prevent stress-induced and aging-related disorders. Overall, this study provides a comprehensive look at the molecular mechanisms by which adaptogens exerts stress-protective effects.

Keywords: Adaptogen; Melatonin; Pathway analysis; RNA sequencing; Rhodiola; Withania.

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