Effects of Corticosterone Therapy on Exaggerated Fear and Mitochondrial Gene Expression Profiles in The PFC and Amygdala of PTSD Model

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INTRODUCTION

Activation of glucocorticoid receptor signaling in the stress response to traumatic events has been implicated in the pathogenesis of stress-associated psychiatric disorders such as post-traumatic stress disorder (PTSD). The metabolic mechanisms underlying the development of exaggerated fear in PTSD are not well defined. In the present study, alterations in the expression of genes associated with mitochondrial functions in the prefrontal cortex and amygdala of an animal model of PTSD were determined. Ingenuity Pathway Analysis (IPA) revealed dysregulated and mitigated signaling networks in the stressed and corticorsterone treated prefrontal cortex and amygdala complex associated with stress response in animal model of PTSD. Thus, informatics of pharmaco-mito-genetic array studies allowed us to determine the detailed mitochondrial focused molecular mechanisms in the prefrontal cortex and amygdala complex of an animal model of PTSD.

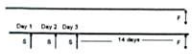
METHOD

Restraint and tail shocks were employed to mimic a substantial extent the pathophysiology of PTSD. Corticosterone treatment and/or stress:□□Stress exposure consisted of a 2-h per day session of immobilization and tailshocks (40 shocks) for 3 consecutive days.

The present study uses a mitochondrion-neuron focused oligonucleotide DNA microarray (rMNChip) to demonstrated(no d) the expression fingerprints of 82 informative genes in the prefrontal cortex of stress group of rats (n=10) in comparison with non stressed control (n=10). Microarray experiments were conducted with both technical and experimental triplicates, resulting in the measurement of expression of each gene 9 times for authentic bioinformatics analysis. Our unsupervised clustering analysis revealed differential expression of 85 genes in the amygdala complex over the control group of rats (n=10).

Prefrontal cortex and amygdala tissue samples were excised from 10 nonstressed control rats and 10 stressed rats, 14 days post stress treatment. Total RNA was isolated, cDNA was synthesized, and gene expression levels were determined using a cDNA microarray.

Fig. 1. Experimental paradigm



RESULTS

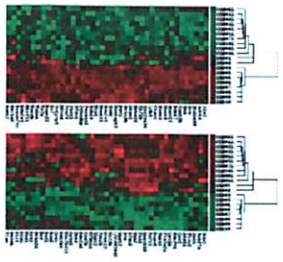


Fig. 2. Dendrograms and Heat maps of selected genes (n=82) in prefrontal cortex of rats (n=20) 14 days after treated with or without stress, based on unsupervised clustering analysis.

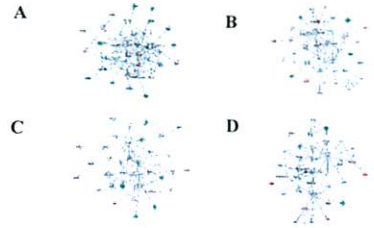


Fig. 3. Four dysregulated signaling pathways in the prefrontal cortex related to stress and fear. Comparison of the expressed genes in stressed (n=10) and control (n=10) prefrontal cortex tissues. The pathway analysis demonstrates the interconnected genes associated with mitochondria functions

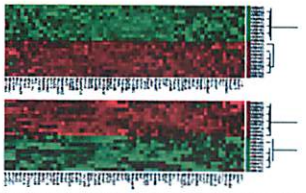


Fig. 4. Dendrograms and heat maps of selected genes (n=128) in prefrontal cortex tissues of rats (n=20) treated with or without corticosterone , based on unsupervised clustering analysis.

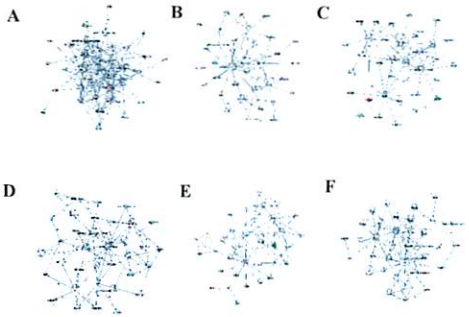


Fig. 5. Six mitigated signaling pathways in the prefrontal cortex related to stress and fear. Comparison of the expressed genes in stressed (n=10) and control (n=10) prefrontal cortex tissues. The pathway analysis demonstrates the interconnected genes associated with mitochondria functions

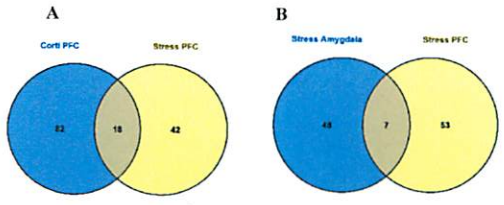


Figure 6 A and 6B, 6A, Venn diagram reveals overlapped genes between stressed and corticorsterone treatment induced genes in the prefrontal cortex 14 days after stress and corticorsterone treatment (n=20). 6B. Venn diagram reveals overlapped genes between stressed induced genes in the prefrontal cortex and amygdala complex 14 days after stress

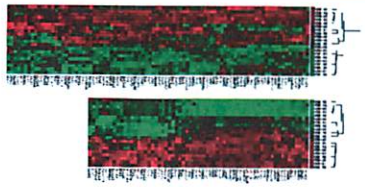
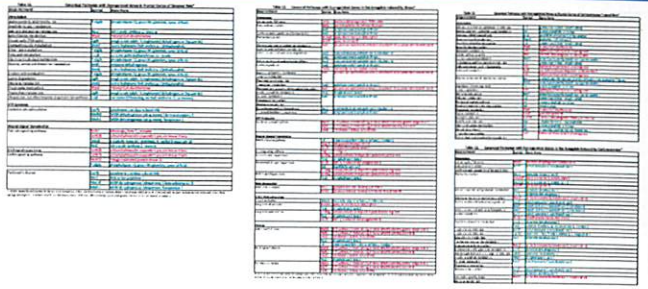


Fig. 8. Dendrograms and heat maps of selected genes (n=152) in amygdala tissues of rats (n=20) treated with or without corticosterone, based on unsupervised clustering analysis.



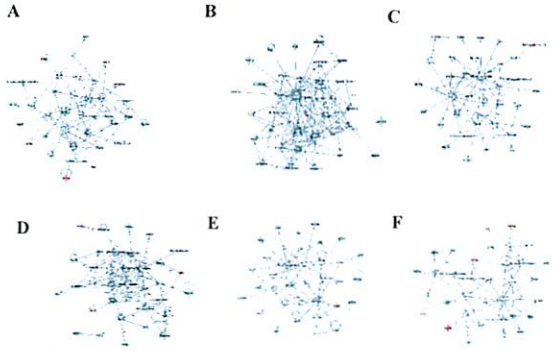
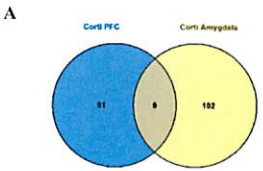


Fig. 7. Six mitigated signaling pathways in the amygdala complex in response to corticosterone treatment. Comparison of the expressed genes in the prefrontal cortex and the amygdala complex in stressed (n=10) and control (n=10). The pathway analysis demonstrates the interconnected genes associated with mitochondria functions



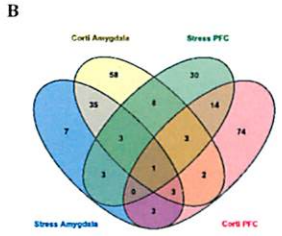


Figure 8A and 8B, 8A, Venn diagram reveals overlapped genes between corticosterone treatment induced genes in the prefrontal cortex and amygdala 14 days after stress (n=20). **8B.** Venn diagram reveals overlapped genes among stressed and corticosterone treatment induced genes in the prefrontal cortex and amygdala complex 14 days after stress

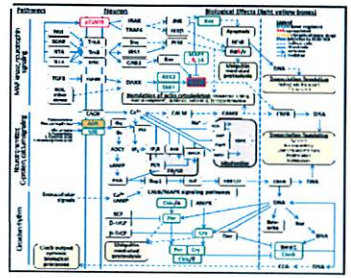


Fig. 9. Neurotransmitter, G-protein, calcium, neurotrophin, MAP-kinase, and circadian rhythms signaling pathways with differentially expressed genes in prefrontal cortex of rats between corticosterone and stress treatments. The mean expression levels, standard deviations, fold changes, p-values, false discovery rate (FDR) and the full name of genes are listed in Table 4. As the diagrams implied, these pathways are highly interactive. The legends at the top right corner explain the relationships among all elements in these pathways. The descriptions in the light yellow boxes illustrate the biological consequences of these differentially expressed pathways

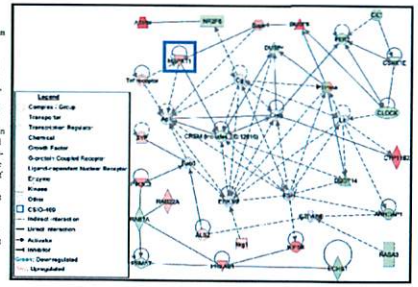


Fig. 10. The molecular networks for neuron function around circadian rhythms proteins. The networks have a total of 35 elements including 13 (37%) upregulated ones, 13 (37%) downregulated, 8 (23%) unchanged, and one complex with partial upregulation and partial downregulation. The mean expression levels, standard deviations, fold changes, p-values, false discovery rate (FDR) and the full name of genes are listed in Table 4. The blue box indicates that the drug CSIO-469 is an inhibitor of mitogen-activated protein kinase 11 (MAPK11). The legends at the bottom left corner explain the interactions among all elements in the molecular networks

CONCLUSION

The current study reveals that multiple signaling networks are up or down regulated in the prefrontal cortex and amygdala circuitry 14 days after traumatic stress. Traumatic stress significantly alters at least 82 genes in the PFC and 65 genes in the amygdala associated with eight pathways related to mitochondria functions. These molecules include well studied and documented networks as well as novel networks that have not been well documented in previous literature. These findings provide a guide for further studies associated with diagnostic biomarkers, therapeutic molecular targets, and identification of optimal strategies for fostering resilience before and after traumatic stress. In addition, current analyses suggest new targets for pharmacological intervention to treat PTSD and fear. These results elucidate the molecular pathways underlying PTSD as a road to diagnosis and treatment. (Supported by CDMRP W81XWH-08-2-0568 and W81XWH-08-006 to H. Li).