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Involvement of the transcription factors NF-kB and Nrf2 in aldosterone induced DNA damage

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Epidemiological studies found an increased risk for kidney cancer in hypertensive patients. These patients frequently exhibit hyperaldosteronism, known to contribute to kidney injury, with oxidative stress playing an important role. We investigated, in vitro and *in vivo*; the capacity of kidney cells to upregulate transcription factors like NF-κB and Nrf2. Aldosterone activated the pro-survival factor NF-κB in vitro and *in vivo* and led to the expression of anti-apoptotic proteins like Bcl-2. The NF-κB-inhibitor PDTC reduced DNA damage in kidney cells. Further, aldosterone activated the regulator of the antioxidative defense, Nrf2 in vitro and *in vivo* and increased the expression of enzymes involved in glutathione synthesis and detoxification. The activation of the two transcription factors was mediated by the mineralocorticoid receptor (MR) and oxidative stress. In vitro, while at 24 h of aldosterone exposure oxidant levels remained high, a decrease in Nrf2 activation, glutathione, and target gene levels was observed. Nrf2 activation therefore could not protect cells against oxidative DNA damage, since aldosterone-induced double strand breaks and 8-oxodG lesions steadily rose. Administration of the Nrf2 activator sulforaphane enhanced the Nrf2 response in vitro and *in vivo* and thereby prevented aldosterone-induced DNA damage. Aldosterone-induced DNA damage triggers the activation of NF-κB and Nrf2. Inhibition of NF-κB, as well as activation of Nrf2 decrease DNA damage.

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Correction of abnormalities in a suite of 900 genes using intranasal vasoactive intestinal polypeptide restores gray matter nuclear atrophy and clinical functioning in Chronic Inflammatory Response Syndrome

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Chronic Inflammatory Response Syndromes (CIRS) are typified by involvement of pro- and anti-inflammatory pathways; coagulation parameters; TGF beta-1; split products of complement activation; autoimmunity; and dysregulation of regulatory neuropeptides, including MSH and VIP. These syndromes are acquired following exposure to biologically produced toxins made by dinoflagellates, cyanobacteria, bacteria, fungi and bacteria among others. The illnesses are multi-symptom and multisystem with a unique group of proteomic findings demonstrated repeatedly in peer reviewed literature. Recently we published CNS abnormalities in NeuroQuant , a volumetric software program most commonly used in patients with traumatic brain injury. The Next Generation RDA Seq testing provided transcriptomic data that added a marked increase to assessment of the overall genomic effect of inflammatory responses seen in CIRS. We report here a group of patients with typical CIRS treated with intranasal VIP who showed (1) correction of typical genomic abnormalities and (2) resolution of gray matter nuclear atrophy seen on NeuroQuant; (3) resolution of persistent symptoms, including executive neurocognitive symptoms. To date these combined findings are not reported in published literature.

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