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Progesterone, Vitamin D, and the Acute Inflammatory Response After Traumatic Brain Injury in the Aged Rat

By

Milos Cekic

Doctor of Philosophy

Graduate Division of Biological and Biomedical Science

Neuroscience

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MA, New York University 1997

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**ABSTRACT**

Progesterone, Vitamin D, and the Acute Inflammatory Response After Traumatic Brain Injury in the Aged Rat

By Milos Cekic

Traumatic brain injury (TBI) is the greatest single cause of death for people in the Western world younger than 45 and a significant cause of death and disability worldwide. The past decade has also seen a 21% increase in TBI events in people over the age of 65, with the mortality rate in this age group more than twice that of young adults. A large amount of recent evidence has shown that treatment with the neuroactive steroid progesterone (PROG) can attenuate many of the pathophysiological events following TBI in young adult animals as well as human patients, but this has not been specifically investigated in the aged. In this series of studies, we extend the potential application of progesterone (PROG) as a treatment for TBI to older subjects by demonstrating its effectiveness in reducing acute inflammation, cell death, and cerebral edema, and improving short-term behavioral outcome in aged rats after bilateral frontal cortical contusion injury. We also show that vitamin D deficiency, which is virtually endemic in the elderly population in industrialized countries and is associated with a number of systemic problems such as cardiovascular disease, atherosclerosis, and cancer, increases baseline inflammation prior to injury, exacerbates the acute inflammatory response to the injury itself, and attenuates the beneficial effects of PROG treatment after TBI in aged rats. These effects can be overcome by co-administration of PROG with 1,25-hydroxyvitamin D3 (vitamin D hormone, VDH), the biologically active form of vitamin D and a neuroactive seco-steroid. Since TBI is a complex process affecting the entire organism and not just the nervous system, with the most common proximate causes of death after injury being edema, sepsis, or overwhelming systemic inflammation leading to multi-organ failure, these results have direct translational implications for treatment and early survival in the elderly human population with brain injury. We show that the endogenous systemic hormonal environment can affect brain injury and treatment outcome, and suggest that combination therapies, especially with pleiotropic agents that affect partially overlapping mechanisms, may be better suited than single targeted agents to the treatment of heterogeneous disease processes such as human TBI.

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O Muse, o alto ingegno, or m’aiutate;

o mente che scrivesti ciò ch’io vidi,

qui si parrà la tua nobilitate.

-Dante, *Inferno II*

“What was that? High C or vitamin D?”

-Groucho Marx, *A Night at the Opera*

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