Traumatic Brain Injury and Aging: Is a Combination of Progesterone and Vitamin D Hormone a Simple Solution to a Complex Problem?

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Summary: Although progress is being made in the development of new clinical treatments for traumatic brain injury (TBI), little is known about whether such treatments are effective in older patients, in whom frailty, prior medical conditions, altered metabolism, and changing sensitivity to medications all can affect outcomes following a brain injury. In this review we consider TBI to be a complex, highly variable, and systemic disorder that may require a new pharmacotherapeutic approach, one using combinations or cocktails of drugs to treat the many components of the injury cascade. We review some recent research on the role of vitamin D hormone and vitamin D deficiency in older subjects, and on the interactions of these factors with progesterone, the only treatment for TBI that has shown clinical effectiveness. Progesterone is now in phase III multicenter trial testing in the United States. We also discuss some of the potential mechanisms and pathways through which the combination of hormones may work, singly and in synergy, to enhance survival and recovery after TBI. **Key Words:** Traumatic brain injury, aging, frailty, progesterone, vitamin D, morphological and functional recovery, systems.

INTRODUCTION

Human traumatic brain injury (TBI) is a notoriously complex and heterogeneous disease process.[1,2] From the initial insult to the highly destructive secondary damage cascade to eventual reorganization and recovery,[3,4] each phase of the injury cascade involves a different set of processes, which sometimes overlap and sometimes do not. At least in part because of this complexity, most drugs designed as monotherapies to modulate single receptors or related groups of mechanisms have failed in clinical trials for TBI, despite showing preclinical promise.[5,6] In addition to the complexity inherent in the injury process itself, the systemic and extraneuronal effects of trauma need to be considered, because these are often the actual causes of death in brain-injured patients.[7]

A variety of additional factors such as age and age-associated systemic alterations can also affect both survival and recovery from severe injury. These include changes in hormonal and drug metabolism, nutritional status, immune function, and increased frailty, among other factors. Given this added layer of complexity, it is not obvious that the injury itself or putative treatments for it will behave in the same way in older subjects as they do in young adults. This population might therefore require not only special research consideration, but also a different treatment paradigm, which could potentially involve combination treatments designed specifically to address an age-altered physiology.

TBI IS A MULTIORGAN SYSTEMIC INFLAMMATORY DISORDER

Acute phase events with the greatest import for survival after TBI appear to be those related to inflammatory processes, especially the production of inflammatory cytokines, which is a well-recognized aspect of the physiological response to trauma.[8] Levels of inflammatory cytokines are the most consistent prognostic markers of outcomes in patients with systemic inflammatory response syndrome, sepsis, multiorgan dysfunction syndrome, and multiorgan failure,[9] all of which are commonly the proximate cause of death after CNS trauma[7,10,11] and generally result from an imbalance between pro- and anti-inflammatory responses to severe injury.[10] We therefore support the view that TBI should be considered a systemic and not just a focal prob-

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lem, especially in the context of inflammation and short-term survival.

Systemic effects are also evident in response to oxidative stress. Shohami et al.[12] reported that TBI induces a cascade of highly reactive oxygen species that can damage brain tissue and other organs throughout the body. Using sophisticated methods to measure the ability of tissue to scavenge free radicals as a measure of oxidative stress, the investigators found that closed head injury in male rats led to widespread changes in brain, liver, lung, skin, kidney, and intestine within 24 h of the insult. More recently Moinard et al.[13] found significantly altered metabolism and mitochondrial activity in the liver triggered by the TBI-induced inflammatory cascade in the brain. Histological examination of liver tissue showed that the TBI caused immune cell infiltration, edema, fibrosis, and necrosis that helped to block normal liver metabolism and homeostasis.

Inflammatory markers are not just causally related to mortality after TBI, but also appear to be a good index of the extent of injury[9,14] and reliable independent predictors of injury outcome.[15–18] Although the levels of the cytokines tumor necrosis factor-α (TNFα) and interleukin-1β (IL-1β) increase after severe injury, it is the level of IL-6 that is considered the most accurate prognostically, because it is the chief regulator of acute hepatic response[19] and correlates with systemic inflammation and outcome.[9] There is also evidence that early increased levels of IL-6 can be a marker of high risk of complication and organ failure.[20] Although it has been argued that systemic inflammation is so complex that it defies traditional reductionist definitions and may not be useful in predicting system behaviors,[21] modulating the production of inflammatory cytokines during the acute phase could be of benefit in reducing mortality and improving the prognosis for better functional outcomes. For example, there is recent evidence of sex differences in patients with multiple trauma, with premenopausal women showing significantly lower plasma cytokines and less multiorgan failure and sepsis, compared with age-matched men.[22] It is possible that these sex differences in response to injury are attributable to higher circulating levels of progesterone (P_4) in female subjects,[23,24] an intriguing hypothesis, given the success of P_4 in treating TBI.

PROGESTERONE AND BRAIN INJURY TREATMENT

A number of recent publications have demonstrated effectiveness of P_4 treatment in experimental models of TBI.[25–29] It has been consistently shown that post-injury administration of P_4 can attenuate the cytological, morphological, and functional deficits caused by traumatic injury.[27,30–35] Unlike other sex steroids, P_4 is synthesized by oligodendrocytes in the brain, where it then acts on membrane-bound and classical nuclear steroid receptors.[36] Progesterone can also affect water channel proteins (aquaporins) to modulate both vasogenic and cytotoxic edema,[37,38] reduce glutamate toxicity, mediate toxic calcium influx by its antagonist effects on sigma receptors, upregulate $GABA_A$ receptors to reduce excitotoxic damage, and reduce apoptosis and necrosis.[29,36] It is likely that the pleiotropic and systemic nature of P_4 is responsible for its effectiveness in the treatment of TBI. As one recent review suggests, "given the multifactorial nature of the secondary injury process, it is unlikely that targeting a single factor will result in significant improvement in outcome. *Conversely, targeting several injury factors may be the most likely therapeutic approach to improve outcome*"[4] (p. 29, emphasis added). Progesterone is just such a multifactorial agent.

The preclinical findings on neuroprotective effects of P_4 have been confirmed in humans in a recently completed phase IIa single-center clinical trial for P_4 in the treatment of moderate to severe adult TBI ($N = 100$).[39] Mortality among patients given P_4 intravenously for 3 days after the injury was less than half that of controls provided standard-of-practice care but no hormone (13.6% *vs* 30.4%). Functional outcomes at 30 days were significantly better for moderately injured patients given P_4 than for the placebo group, and a data safety monitoring board appointed by the U.S. National Institutes of Health found no serious adverse events attributable to P_4 treatment. This was the first successful clinical trial for the treatment of TBI in more than 30 years of research.

A second independent, randomized double-blind study from China examined P_4 in 159 patients with severe TBI given an intramuscular course of P_4 treatment over 5 days. Similar beneficial outcomes on morbidity and mortality were observed at both 30 days and 6 months after injury, again without any serious adverse events caused by the treatment.[40]

A phase III, 17-center, double-blind, randomized clinical trial for TBI will start enrolling about 1000 patients in January 2010 (NCT00822900; http://www.clinicaltrials.gov).

One specific reason for increased survival in P_4-treated TBI patients may be the ability of P_4 to substantially reduce systemic acute-phase inflammation and so prevent multiorgan dysfunction syndrome and multiorgan failure. In support of this idea, Chen et al.[41] found that contusion injury to the cerebral cortex in rats induced expression of IL-1β and TNFα in the intestinal mucosa, followed by apoptosis in the intestinal mucosa. A 5-day course of treatment with P_4 reduced both the cytokines and cell death in the intestine, demonstrating the systemic benefits of P_4 administration.

AGING AND BRAIN INJURY

Although the incidence of TBI has decreased in most age groups because of improved primary prevention (such as seat belt and safety helmet use), it has increased by 21% in people over the age of 65.[42] Age is itself an independent predictor of mortality due to TBI, which in the geriatric population is twice that of younger age groups.[43] The age distribution of hospitalizations due to TBI has the most pronounced peak late in the eighth decade,[44] and the highest mortality rates from TBI, ranging from 60.9% to 86.8% depending on the study, occur in people 75 to 80 years old.[45] Given the magnitude of the problem, it is important to address the effectiveness of any treatment specifically in aged subjects.

Old animals are fatter, more sedentary and irritable, and (like most old people) have sensory, cognitive, and motor deficits that can exacerbate injury-induced impairments and impede functional recovery. Old rats and old people also metabolize drugs differently than young ones, so doses and agents that work in younger subjects might not work in older animals, or could even aggravate the injury. A number of systemic physiological changes associated with the aging process could also alter drug effectiveness, such as altered metabolism and endogenous hormonal milieu,[46–50] impaired immune function,[51–53] increased levels of systemic inflammation,[54] and reduced physiological reserve or frailty.[55,56] Additional changes within the CNS, including reduced plasticity[57] and more subtle chemical, structural, morphological, and network alterations,[58,59] can also significantly affect the ability of an older animal or person to survive and recover from severe injury.

CNS effects of aging

Although it is established that there is no overt loss of neurons in the brain with normal aging, a number of more subtle structural, chemical, and metabolic changes occur,[58,59] both at the level of individual neurons and in medium-scale neuronal networks, that can significantly affect the ability of the CNS to adapt to internal and environmental changes. Other changes in the CNS in response to aging are similar to the changes that occur in other cells, and include increased oxidative stress, altered protein accumulation, nucleic acid damage, and dysfunction of energy homeostasis.[59] The cellular changes during normal aging make neurons increasingly susceptible to excitotoxic damage[59] through the impairment of ion pumps,[60] dysregulation of Ca^{2+} homeostasis,[59] and decreased mitochondrial function.[61] Given that all these processes are involved in the evolution of the injury after traumatic insult, the process of aging itself could significantly increase vulnerability and impair the potential for recovery from TBI in aged individuals.

There is evidence that the brains of aged animals exhibit gene expression profiles characteristic of microglial activation and neuroinflammation.[62–65] Microglia themselves also appear to respond to stimulation with an amplified inflammatory response in aged animals.[66] This neuroinflammatory priming can significantly affect the development of neurological dysfunction. Under normal conditions these inflammatory changes are temporary, and the microglia return to a dormant state as soon as the immune challenge is resolved. Aging, however, creates a brain environment in which microglial sensitivity to immune activation is increased and microglial activation does not resolve, which can lead to the pathogenesis of neurological disease.[66] This situation is likely to exacerbate secondary injury in older subjects after TBI, in that trauma can lead not only to a severe systemic immune response,[67] but also to immune factor release from the damaged cells within the brain itself.[68]

Exaggerated neuroinflammation can also interfere with neuroplasticity during the recovery phase, and inflammatory cytokines such as TNFα, IL-1β, and IL-6 appear to directly interfere with long-term potentiation,[69–71] memory consolidation,[72] neurite outgrowth,[73] and hippocampal neurogenesis.[74] These data suggest that continued presence of reactive microglia in the aged brain creates an environment permissive to a prolonged and amplified neuroinflammatory response that can lead to subsequent complications, especially after TBI.[66]

Systemic effects of aging and immunosenescence

In addition to alterations in the CNS, age-related changes in the immune system are also common and have been implicated in virtually all age-associated disease processes.[53] Aging is associated with a general activation of the inflammatory response, which, because of the chronic antigenic stress on innate immunity experienced over a lifetime, becomes the basis for the onset of inflammatory diseases[51] and an increasing inability to mount an appropriate immune response to antigenic stimulation.[53] With aging there is also a decrease in the production of anti-inflammatory hormones,[75] as well as a general tendency toward production of elevated amounts of proinflammatory cytokines by peripheral blood mononuclear cells.[54]

The fulminating inflammatory state associated with increasing age has been dubbed *inflammaging*.[54] This condition is systemic but also has specific effects within the CNS.[66] Given the importance of inflammatory cytokines such as TNFα, IL-1β, and IL-6 in both behavioral modulation and the evolution of traumatic injury, it is likely that an increased neuroinflammatory cytokine response in the elderly patient can disrupt neuronal synaptic plasticity, establishing a CNS environment predisposed to long-lasting complications, as well as a reduced ability to recover from trauma.[66] In fact, the aged brain appears to exist in a chronic state of inflammation that is associated with increased immune reactivity and contin-

uous low-level production of central inflammatory cytokines.[68]

Endocrine effects of aging

In addition to structural and immune decline, human aging is associated with decreased activity in a number of systemic hormones, including thyroid hormone,[47] sex steroids,[46,49,76] growth hormone,[48] insulin-like growth factor type 1 (IGF-I),[48] and 25-hydroxyvitamin D_3.[77,50,78] Especially intriguing is the relationship between endocrine decline and the change in immunological function. Some research suggests that proinflammatory cytokines may downregulate the physiological responses to a variety of hormones, including insulin, growth hormone, IGF-I, thyroid hormone, and estrogens.[79]

TNFα, IL-1, and IL-6 can specifically modulate the release of growth hormone, growth hormone releasing hormone, and somatostatin,[80] and are known to reduce concentrations of IGF-I[81] and increase the concentrations of glucocorticoids[82] in the serum of human patients. Lower serum IGF-I and dehydroepiandrosterone sulfate levels were found in frail (compared with nonfrail) elderly individuals,[56] and an inverse correlation between serum IL-6 and IGF-I was noted only in frail individuals.[56] Elevated levels of inflammatory cytokines[83–86] and the development of frailty in older adults[87,88] have also been associated with vitamin D deficiency (D-deficiency).

These data can be taken to suggest that the immune system and its age-associated dysfunction may be intimately related to the functioning of the neuroendocrine system, and that this relationship may further contribute to the development of systemic insufficiency and vulnerability to injury.

Aging and vitamin D deficiency

Of all the endocrine and nutritional disruptions that affect the elderly population, D-deficiency has recently received considerable attention, partly because an estimated 1 billion people worldwide exhibit D-deficiency or insufficiency.[89] In the northeastern United States, studies show a prevalence from 32% in healthy adults[90] to approximately 50% for adolescents and preadolescents.[91–93] The most dramatic statistics for D-deficiency, however, come from studies in the elderly population, which show that 40 to 100% of community-dwelling American and European older men and women are D-deficient. Even higher averages are seen in the ill and institutionalized.[94–102]

Vitamin D-deficiency has been associated with many systemic disorders, including infectious, inflammatory, and autoimmune conditions,[103–109] cardiovascular disease,[110,111] hypertension and atherosclerosis,[112] neuromuscular function,[113] cancer,[114] neurodegenerative diseases,[115,116] and neuropsychological and functional outcomes in the elderly population.[117] In fact, D-deficiency appears to be correlated with many if not most of the problems associated with advanced age, especially those with an inflammatory component.[103,106] There is also evidence that the level of serum vitamin D is a key marker of frailty,[83,88] and that it is associated with elevated levels of IL-6.[118]

It is worth noting here that vitamin D is in fact not a vitamin, but rather a secosteroid hormone with the same cholesterol backbone as other steroids (including P_4) and with its own class of nuclear steroid receptors and signaling mechanisms.[119,120] In its biologically active form, 1,25-dihydroxyvitamin D_3 (vitamin D hormone, or VDH) is a hormone with sites of action throughout the CNS; it can be considered a neuroactive steroid, because it is both synthesized and has actions in the nervous system. Vitamin D hormone is also a known and potent modulator of the cell cycle, immune function, and calcium homeostasis. As such, it may be in important compound not only as an endogenous hormone, but also as a treatment in its own right, especially in combination with P_4.

AGING, BRAIN INJURY, AND NEUROSTEROIDS

Progesterone in aged rats

Given the promising results with progesterone in young adult animals, we sought to determine if it would work as well in aged animals.[121] The working hypothesis in our aging studies was that P_4 would be effective in treating TBI in aged rats. We measured levels of inflammatory proteins, cell death, edema, and behavior during the acute phase of injury (24–72 h after TBI) in aged rats (20 months old, approximately equivalent to 60 years in humans) to determine the potential of P_4 in reducing mortality after TBI. Injured animals treated with 8 mg/kg and 16 mg/kg P_4 beginning within the first hour after surgery showed decreased expression of cyclooxygenase-2, IL-6, and nuclear factor κB (NFκB) at all time points examined, indicating a reduction in the acute inflammatory process compared with the aged rats given vehicle. The 16 mg/kg P_4 group also showed reduced neuronal apoptosis at all time points, and decreased edema and improved locomotor outcomes. Although the lowest P_4 dosage used in previous studies in younger animals (8 mg/kg) was effective in the aged animals, overall it was not as effective as 16 mg/kg, suggesting potentially altered P_4 kinetics and metabolism in the older animals.

We also observed an association between increased levels of P-glycoprotein and reduced edema, suggesting that P_4 may reduce cerebral edema both through its anti-inflammatory effects on cytokine levels and through direct effects on the integrity of the blood–brain barrier. P-glycoprotein is regulated through the pregnane X re-

ceptor (PXR)[122,123] and plays a critical role in removing toxic products from the cell. Progesterone has been shown to exert neuroprotective effects through the PXR.[124] This raises the intriguing possibility that some of the post-TBI benefits of P_4 may be effected through this relatively novel signaling mechanism.

Consequences of D-deficiency for TBI and P_4 treatment

Given the effectiveness of P_4 in aged rats after TBI and the prevalence of D-deficiency in the elderly population, we asked whether D-deficiency would affect the outcome of a brain injury and whether it would interfere with the benefits of P_4 treatment in aged rats. Based on the current literature, we hypothesized that D-deficiency would exacerbate inflammation and reduce or eliminate the benefits of P_4 treatment after TBI in aged animals. Because early onset of inflammation is taken as a reliable prognostic indicator of mortality in human patients with significant trauma, we measured acute inflammatory proteins, cell death, DNA damage, and short-term behavior as indicators of inflammation and secondary damage in D-deficient aged animals after TBI.

In general, we observed increased inflammation in aged rats with D-deficiency, whether our subjects were uninjured, injured but untreated, or injured and treated with P_4.[125] Our results confirmed previous studies[103,106,126] suggesting that D-deficiency establishes a higher baseline level of inflammation, in effect priming the system for an increased immune–inflammatory response after brain injury. This elevated acute-phase response correlated with increased cell death and DNA damage, indicating a more severe secondary injury process. Vitamin D deficiency also affected sickness behaviors, such as movement and grooming, which strongly correlated (by general linear models) with the expression of TNFα and IL-6.

Our data can be taken to indicate that short-term alterations in locomotor behavior could serve as a rough behavioral indicator of brain inflammation in the acute phase after injury. Our models also indicated that both TNFα and IL-6 were significantly increased by D-deficiency and that both cytokines showed deficiency–treatment interaction effects. We take this to mean that the increased expression of these inflammatory cytokines may play an important role in the cascade of toxic mechanisms underlying the attenuation of P_4 benefits in D-deficiency. Also notable is the fact that, although most of the variability in TNFα was accounted for by injury, the level of IL-6 was affected primarily by D-deficiency. This fits with other independent data connecting IL-6 levels with D-deficiency, frailty, and inflammation[88,118,127,128] and suggests to us that IL-6 may be the key cytokine involved in the detrimental effects of D-deficiency. The elevation in IL-6 was most evident in our data comparing D-deficient and D-normal animals after TBI and P_4 treatment. Most of the other cytokines were elevated in D-deficient animals twofold or threefold, but IL-6 was increased nearly fivefold by 72 h after injury.

Management of VDH deficiency

Given the data from human studies showing that the level of IL-6 is the most accurate prognostic indicator of survival in the acute phase after TBI, our findings could have significant implications in the clinical setting. We suggest that elderly people be screened for potential D-deficiency and provided with supplementation therapy after TBI, because they could be more frail and thus more likely to die from their injuries. Powner et al.[129] point out that, during rehabilitation from severe TBI, as many as 40% of patients suffer from endocrine dysfunctions associated with sickness behaviors such as chronic fatigue, decreased libido, amenorrhea, increased anxiety, memory failure, depression, and anorexia, among others. Although for some of these symptoms it is speculative that vitamin D could be a helpful treatment, the costs of vitamin D supplementation are minor and it is easy to give, and the implications for the treatment of a number of disease conditions could be important for clinical practice.

Although it seems reasonable that supplementation with vitamin D in a deficient state would be equivalent to ongoing vitamin D sufficiency (i.e., acute correction of deficiency should be equivalent to no deficiency), there is no a priori reason to make this assumption. At 24 h after injury, we observed no differences in inflammatory cytokines between VDH-treated deficient and D-normal animals. By 72 h after injury, while there was still no difference with TNFα and IL-1β was still lower than in D-normal animals, levels of IL-6, NFκB p65, and cell death were all higher in VDH-treated deficient than in D-normal animals. These findings can be taken to suggest that, at least with reference to IL-6 levels, acutely correcting D-deficiency is not as good as maintaining D-normal status. In other words, prevention could be better than acute treatment.

Vitamin D deficiency as a public health issue has received much attention recently in the popular press, as well as in the medical literature. Now we can add another benefit to maintaining a normal vitamin D status: it is not just good for the arteries and protective against cancer, it can also be a primary intervention against TBI—in some ways, the equivalent of wearing a seatbelt. Although further research needs to be done on this issue, we suggest that the findings are likely to apply across the developmental spectrum and not just to the elderly population (where it might be exacerbated because of complications from other health-related factors).

COMBINING P_4 WITH VDH IN TREATING TBI IN THE AGED POPULATION

Rationale for combinatorial therapy in treating TBI

Combination therapy is somewhat new to the area of brain injury, but it is a well-established pharmacological approach to a number of other diseases, such as HIV–AIDS or tuberculosis, although most drug development still focuses on individual drugs targeting one or at most a few specific mechanisms. Two issues are involved: drug combination and target promiscuity, or *pleiotropy*.

Rationales for combining drugs include targeting multiple divergent mechanisms and overcoming single-drug limitations such as receptor kinetics, pharmacology, and signaling pathways.[130,131] This idea has recently gained ground in the treatment of TBI.[5] Because both P_4 and VDH are pleiotropic and multifunctional, it is difficult to predict specific mechanisms of interaction, but both could be used to target cell death after TBI, for example, as one of the many mechanisms by which a brain injury evolves. On the one hand, P_4 would reduce cell death by preventing release of cytochrome c from the mitochondria, upregulating the antiapoptotic Bcl-2 protein, and downregulating the proapoptotic Bax protein.[1,26,132] Vitamin D hormone, on the other hand, would prevent the reactivation of cell cycle machinery,[133–135] which is a common step toward apoptosis in terminally differentiated neurons,[136,137] and would upregulate nerve growth factor (NGF), providing a strong external prosurvival signal.[138,139] The two compounds would thus act in synergy and provide benefits greater than either compound alone.

Combining P_4 and VDH, pleiotropic drugs that work primarily through intracellular receptors and transcription factors likewise merits serious consideration, as meeting the criteria posited by Vink and Nimmo[4] in their review of multifunctional drugs for head injury. We strongly agree that a combinatorial approach to treatment is not only reasonable but may be essential, given the complexity and heterogeneity of human TBI and the fact that, of the 130 preclinical monotherapy drugs that have shown promise in treating brain injury, all have failed when taken to clinical trial.[5]

Effectiveness of P_4–VDH combination after TBI in aged rats

We recently demonstrated effectiveness of a combination of P_4 and VDH in both *in vitro* and *in vivo* models. Combining VDH and P_4 was shown to be effective *in vitro* in increasing the survival of primary cortical neurons under glutamate challenge, with the combination showing more neuroprotection than either compound alone at best dose.[140] We applied the same treatment concept to D-deficient aged rats with TBI and showed that the only treatment that reduced proteins measured (TNFα, IL-1β, IL-6, NFκB p65, activated caspase-3, and p53) in all cases by 72 h after injury was the combination of P_4 and VDH (5 mg/kg in a single dose) compared with vehicle or either compound given alone. The combination treatment was also the only one that dramatically improved behavioral parameters, which our statistical models again showed to be strongly correlated with systemic inflammation and levels of TNFα and IL-6. Should these results be translatable to humans, the clinical implications are obvious: a combination treatment of P_4 and VDH given to elderly patients with TBI should improve survival over P_4 given alone to the same population.

Briefly summarized, we conclude that 1) in aged rats with brain injury, P_4 is effective in reducing acute inflammation, a key indicator of survival in human patients; 2) D-deficiency increases acute-phase inflammation and attenuates the benefits of P_4 treatment in aged rats with TBI, suggesting that such a deficiency could increase mortality after brain injury in human patients; 3) a combination of P_4 and VDH partially reverses the effects of D-deficiency and reduces post-TBI acute inflammation in aged rats, suggesting that, should these results translate to the clinic, a simple vitamin D injection combined with P_4 could help save many human lives. Vink and Nimmo[4] address this theme directly:

> The brain is the most complex organ in the body, and significant gaps still exist in our understanding of normal brain function and how it is affected by acute injury. Unlike other organ systems, we cannot readily relate cellular function to the function of the organ as a whole . . .. Nonetheless, we do understand that acute brain injury is a heterogeneous type of injury, made up of immediate and delayed anatomic, molecular, biochemical and physiological events that are both complex and multi-faceted. So complex are these interactions that the concept of a single magic bullet is no longer accepted by the research community, and the focus has now turned to interventions that can modulate a number of independent injury factors simultaneously [p. 37].

Potential mechanisms of action

Although P_4 acts through a number of mechanisms to reduce cell death and improve functional recovery after TBI,[36,141] here we propose that a key process in its ability to reduce inflammation after injury is the ability to inhibit proinflammatory Th1 and also stimulate anti-inflammatory Th2 immune responses. Although the Th1/Th2 paradigm is not unproblematic,[142] it is useful in understanding the role of the adaptive immune system in inflammation. Our explanatory model is based on the fact that Th1/Th2 differentiation marks a decisive event very much like a phase transition in the development of extended inflammation after severe injury.

As suggested earlier, this reduction in systemic inflammation may be one of the key mechanisms by which P_4

significantly increases survival after TBI in human patients.[39,40] With age, the general response of the immune system moves toward a proinflammatory condition[54,66] that is associated with frailty and the increased susceptibility of aged organisms to external insult.[55,56,143] This fact of increased inflammation and decreased immune flexibility with age could explain why we needed a larger dose of P_4 in older animals to obtain similar effects on acute-phase reactants. In other words, anti-inflammatory effects need to be maximized to overcome the underlying predisposition toward inflammatory hyper-reactivity.

Under conditions of D-deficiency, the proinflammatory Th1 bias is elevated to a point at which P_4 alone cannot counteract the amplification of the inflammatory cascade after injury. One way to prevent overwhelming inflammation after injury, then, is to combine pleiotropic drugs such as P_4 and VDH. Although the various gene regulatory and signaling mechanisms will be different, they will presumably synergize at the systemic level to inhibit Th1 differentiation, reduce the acute phase, and potentially improve outcome and survival.

CONCLUSION

A general approach to conceptualizing aging views it as a loss of systemic integration and adaptability that leads to a reduced ability to resist environmental perturbation, eventually leading to death.[144] This decline of complex functioning in aging and disease has been observed in various systems, from cardiac rhythms and gait to cerebral autoregulation and large-scale brain network integration.[145–151] Because of its association with frailty and various other age-related diseases, D-deficiency appears to have a similar destabilizing effect.[83,152] Progesterone and especially VDH can be viewed as system stabilizers, as is evident from their beneficial effects on processes that range from DNA stability and cell cycle control to systemic immune function and hormone production.[50,133,153] Because severe TBI is essentially a massive perturbation that leads to activation and likely extreme overactivation of defensive responses (as in the case of inflammation, which although beneficial in the short term can also be highly damaging when overactive or prolonged), the introduction of stabilizing factors may allow for a reduction of this early damage and an improved ability to recover.

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