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Combination Treatment with Progesterone and Vitamin D Hormone May Be More Effective than Monotherapy for Nervous System Injury and Disease

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Abstract

More than two decades of pre-clinical research and two recent clinical trials have shown that progesterone (PROG) and its metabolites exert beneficial effects after traumatic brain injury (TBI) through a number of metabolic and physiological pathways that can reduce damage in many different tissues and organ systems. Emerging data on 1,25-dihydroxyvitamin D_3 (VDH), itself a steroid hormone, have begun to provide evidence that, like PROG, it too is neuroprotective, although some of its actions may involve different pathways. Both agents have high safety profiles, act on many different injury and pathological mechanisms, and are clinically relevant, easy to administer, and inexpensive. Furthermore, vitamin D deficiency is prevalent in a large segment of the population, especially the elderly and institutionalized, and can significantly affect recovery after CNS injury. The combination of PROG and VDH in pre-clinical and clinical studies is a novel and compelling approach to TBI treatment.

Keywords

1, 25-dihydroxyvitamin D_3; combination therapy; neurosteroids; progesterone; traumatic brain injury; vitamin D

1. Introduction

In the past twenty years, dozens of phase II and III clinical trials for moderate and severe traumatic brain injury (TBI) have failed. This is in spite of the fact that over 130 drugs have shown some efficacy in animal models of injury [174]. One major reason cited for these disappointing outcomes is that the complex and varied mechanisms associated with different types of TBI are not being addressed by a single drug targeted towards only one or a few receptor sites. While pre-clinical experiments use mostly tightly controlled studies with well-circumscribed injuries and clearly defined outcomes, the pathophysiology of TBI in humans is often much more heterogeneous and systemic, affecting many different tissue systems and not just the brain itself. Treating patients suffering from a constellation of these

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injury-induced events may require a pleiotropic agent or a combination of drugs that can act simultaneously or even sequentially on the injury cascade without producing serious adverse events and complications.

Pre-clinical and clinical data accumulating over the last several years indicate that progesterone (PROG) may be highly effective in the treatment of TBI [91,246,255,259,300,302]. A neuroactive steroid, PROG has been shown to improve behavioral and functional recovery and to reduce inflammation, oxidative damage, cerebral edema, and neuronal cell death [64,102,114,299]. Although specific modes of action have yet to be completely defined, PROG has been shown to lead to improvements via a variety of molecular mechanisms [221,244,280], making it likely that interacting pleiotropic actions are responsible for its observed benefits. PROG is therefore a hormone with multiple mechanisms of action and can even be considered a “combination therapy” in itself [174]. Given its demonstrated effectiveness and safety in human patients, it is reasonable to consider PROG as a basis for combinations with other potential therapies.

In this respect it is logical to ask first what contextual conditions might limit the beneficial effects of the hormone in a clinical setting. In other words, what co-morbid conditions might affect TBI patients that could reduce the ability of PROG, or any other drug, to promote recovery? Recent research suggests, for example, that vitamin D deficiency (D-deficiency) can exacerbate injury and potentially reduce the beneficial effects of other treatments for TBI [39,180]. This is especially the case in older subjects and is no small problem, because it has been reported that well over half of older adults suffer from D-deficiency [206]. There is also increasing evidence that about 30-35% of the general American public also suffers from D-deficiency, so patients of any age, including children, presenting with a TBI might be placed more at risk and have a less favorable outcome if they are D-deficient. In this context something as simple as providing vitamin D supplementation could improve recovery and potentially enhance the neuroprotective benefits of PROG (or any other) treatment. This could be important from a clinical perspective, given that most elderly patients who come to the hospital, with or without TBI, will be D-deficient.

Furthermore, it is becoming apparent in the wake of the failure of most TBI treatment clinical trials that multi-targeted pharmacotherapies hold more promise than drugs targeting specific pathobiological pathways [196] and that treatment may be optimized by combinations of agents acting on different mechanisms or the same mechanisms differently [76,92]. The concept of multi-therapy has already become a standard approach for HIV/AIDS treatment, and patients are known to respond much more effectively to combinations of drugs, each targeted to different parts of the disease cycle, acting at different sites, and synergistically enhancing potencies and durations of action. The same approach has been suggested for TBI, especially due to its complex manifestation in human patients [174], where the functions of multiple organ systems may be affected by a direct injury to the brain.

Based on the literature, we suggest that 1,25-hydroxyvitamin D_3 (or vitamin D hormone, VDH) is potentially a good candidate for a combination agent to be used in conjunction with PROG, since both hormones have high safety profiles, act on many different injury and pathological mechanisms, are readily available, easy to administer, and relatively inexpensive. In this article, we review the evidence for PROG neuroprotection after TBI and the emerging evidence for VDH as a neuroprotective agent, and discuss whether combining the two would be a good step to take in the development of a novel therapy for TBI.

2. Progesterone and Traumatic Brain Injury

2.1. Progesterone and Traumatic Brain Injury in Human Patients

A number of recent publications have demonstrated effectiveness of PROG treatment in experimental models of TBI and stroke [244,254,255,258]. Based on the mounting positive pre-clinical data, two single-center Phase II clinical trials using PROG to treat TBI were recently completed, with promising results. The ProTECT ("Progesterone for Traumatic Brain Injury, Experimental Clinical Treatment") trial was a randomized, double-blind, placebo-controlled trial of 100 patients with moderate to severe brain injury (Glasgow Coma Scale (GSC) scores of 4-12) performed at Grady Hospital in Atlanta, Georgia, a Level I trauma center [300]. No adverse effects were observed, and the severely injured patients receiving three days of intravenous PROG beginning 6-8 hours after injury showed a greater than 50% reduction in mortality at 30 days over those receiving placebo. The moderately injured group also showed statistically significant "encouraging signs of improvement" on Disability Rating Scale outcome compared to controls at 30 days. The conclusion was that PROG helped patients with both severe and moderate injuries, but that the effect was confounded in the severely injured by the fact that many in the group given PROG survived who otherwise would not have, so the overall recovery process took longer than for the moderately injured group.

These results were supported by another single-center trial of 159 severely brain-injured subjects (GCS ≤ 8) [302] in which patient outcomes were tracked for a longer time. The patients in this study received a five-day treatment with intramuscular injections of PROG within 8 hours of injury and showed substantially better survival and functional outcomes at both 3 and 6 months than controls. It is important to note that in both studies, PROG not only decreased mortality, but significantly enhanced functional outcome measures. The patients did not just survive to be consigned to a vegetative existence. Although these two reports need to be confirmed in larger multi-center studies, taken together they are the first to show a substantial benefit for TBI in human patients [65], making PROG among the most promising of the candidates that have been proposed [279].

2.2. Progesterone Signaling Mechanisms

PROG is produced by the ovaries and the corpus luteum in females during normal reproductive cycling [244] and by the adrenal glands, which are its main source in men [225]. PROG is also locally synthesized in both the peripheral and central nervous systems by neurons and glia, and its synthetic enzymes, cytochrome cholesterol side-chain cleavage enzyme (P450scc), which generates pregnenolone from cholesterol, and 3β-hydroxysteroid dehydrogenase (3β-HSD), which synthesizes PROG from pregnenolone, are both present throughout the brains of animals as diverse as fish and humans [103,187,188]. This makes it a neuroactive steroid, or "neurosteroid," defined as a steroid hormone that is synthesized in and has effects on the nervous system [12].

Like all steroids, PROG exerts its cellular effects by regulating gene transcription in the nucleus. These "classical" actions are mediated by the cytoplasmic progesterone receptor (PR), which occurs in two main splice isoforms, PR-A and PR-B. Ligand binding to these receptors recruits nuclear receptor coregulators such as members of the steroid receptor coactivator (SRC) family, which have been found to be limiting factors in steroid-induced responses in the brain [37]. The entire complex then migrates to the nucleus, where it binds to progesterone response elements (PREs) in the promoters of genes and initiates or inhibits gene expression. The PR is also capable of interacting with the Src tyrosine kinase family in the cell membrane [68].

In addition to the classical cognate PR, PROG also interacts with other signal transduction mechanisms such as the σ1 receptor, for which it is a competitive inhibitor and through which it may reduce N-methyl-D-aspartate (NMDA) glutamate signaling [15,111]. PROG also signals at the nicotinic acetylcholine receptor (nAChR) [276] and affects gamma-aminobutyric acid (GABA), the main inhibitory transmitter in the brain, through its 5α-reduced metabolite allopregnanolone (or 3α,5α-tertrahydroprogesterone; ALLO) and positive modulation of the $GABA_A$ receptor [13]. Both these mechanisms may be responsible for the neuroprotective effects of PROG, as they inhibit the excitotoxic response to injury. PROG metabolites have indeed been shown to be neuroprotective in their own right in models of kainic acid-induced hippocampal injury [44,45] and after experimental TBI [63,64,280]. PROG is also known to activate the pregnane X receptor (PXR), which may also be responsible for some of its protective effects in addition to those achieved through the PR. Finally, recent evidence suggests that PROG may also exert direct signaling effects through activation of a membrane surface receptor, the 25-Dx [104,185].

All these modes of action—gene transcription, neurotransmission, and signal transduction—are affected by PROG, and are likely to be responsible for its effects in the nervous system. Further complexity is added by the fact that both the synthetic enzymes and receptor/signaling systems are modulated by physiological context such as injury and, potentially, aging [244]. For example, not only may receptors be upregulated (25-Dx) or downregulated (PR) in response to TBI, but certain genes affecting neuronal functioning may develop responsiveness to PROG only after injury [56,243,244].

2.3. Progesterone as a Neuroprotective Agent

One reason PROG shows benefits where other drugs have failed is that it is a pleiotropic drug. Attention was first drawn to PROG as a treatment for TBI when it was observed that females exhibited less edema after injury than males, with pseudopregnant females (high in PROG) exhibiting virtually none [6,234]. A number of subsequent studies have shown that PROG can reduce edema and excitotoxic cell death in the perilesional area of secondary injury [114], and protect against ischemia [52,240]. One major problem with central nervous system (CNS) damage (in both TBI and stroke) is disruption of blood flow to the local area of injury, leading to loss of oxygen and glucose, energy failure, and eventual cell death. PROG has been shown specifically to protect neurons against cerebral ischemia [33,97] and to decrease infarct size [130,146]. There are several observed effects in this resistance to ischemia: 1) maintenance of mitochondrial function, 2) increased pro-survival signaling, and 3) reduced internal and exogenous pro-apoptotic signaling [3,33,97,240,244]. PROG appears to affect mitochondria in multiple ways. It restores them to normal morphology even after severe vacuolation [56], it inhibits pro-apoptotic cytochrome c release [239] and it upregulates the expression of anti-apoptotic mitochondrial proteins such as B-cell lymphoma 2 (Bcl-2) while decreasing the levels of pro-apoptotic signals such as Bcl-2-associated X protein (Bax), Bcl-2-associated death-promoter (BAD), and caspase-3 activation [3,63,83,205,298,305]. PROG may affect the expression of these proteins through activation of the extracellular signal regulated kinase (ERK) signaling pathway, which phosphorylates the cyclic adenosine monophosphate (cAMP) response element binding protein (CREB), upregulates bcl-2, and confers improved resistance to ischemia [77,78]. PROG and its metabolites have also recently been shown to modulate mitogen-activated protein kinase (MAPK) and phosphoinositide-3 kinase (PI3K) signaling in the hypothalamus, hippocampus, and cerebellum of ovariectomized rats *in vivo* [105]. Finally, PROG has also been shown to reverse the alterations in mitochondrial respiration [229] and normalize the expression of the Na^+,K^+-ATPase in experimental autoimmune encephalomyelitis (EAE) and models of spinal cord and nerve crush injury [82,149,231]. Since both of these are important issues in the energy failure and loss of ionic gradients that

lead to cell death, this normalization of cellular metabolism is a key step in the attenuation of secondary injury.

Increased survival of glial and neuronal cells is associated with elevated levels of trophic factors. PROG has been shown to increase levels of both nerve growth factor (NGF) [213,272] and brain-derived neurotrophic factor (BDNF) [95,96,241] after injury. These proteins are especially necessary for glial survival and remyelination [150,244]. Most importantly, however, PROG is known to reduce microglial activation and the production of pro-inflammatory and pro-apoptotic cytokines such as tumor necrosis factor α (TNFα) and Interleukin-1 (IL-1) [66,114,190,221]. This is very significant, since prolonged inflammation is the main cause of extended secondary injury [19,193,247]. PROG also inhibits activation of complement factors [221,280], and modulates the coagulation cascade [281], both of which are important mechanisms of inflammatory amplification. PROG has also been shown to push helper T cell (T_H) cell differentiation towards the T_H2 phenotype, which may also play a role in its anti-inflammatory activity [178].

Improvement of mitochondrial function, increased pro-survival factors, and reduced inflammation are not only beneficial in the injury penumbra but have important systemic effects. TBI-associated systemic inflammation is a key mechanism in mortality, and can lead to multi-organ failure and infection [154,312]. After TBI, catecholamine-induced necrosis of cardiomyocytes leads to cardiopulmonary dysfunction and is also a significant cause of mortality [312]. A compound like PROG that increases survival signaling and attenuates inflammation has a role in recovery that extends well beyond the brain [40,219].

There is also evidence that PROG treatment after TBI reduces lipid peroxidation [235], perhaps through upregulation of antioxidant enzymes such as superoxide dismutase (SOD) [191], although the mechanisms of action are not completely understood [244]. A reduction of the damage caused by reactive oxygen and nitrogen species (ROS/RNS) can improve cell survival by maintaining membrane integrity, and helps to maintain the blood-brain barrier (BBB) by limiting oxidative damage to the endothelium. PROG has also been shown to help maintain BBB function by upregulating P-glycoprotein (Pgp), an efflux pump transporter and marker of BBB health that serves to eliminate xenobiotic and toxic substances; in the case of traumatic injury, these consist of inflammatory cytokines and ROS-producing compounds [53]. PROG can also protect neurons from direct toxicity of glutamate, $FeSO_4$, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and β-amyloid [26,98,205,210], the last two of which may have implications for the development and prevention of Parkinson's and Alzheimer's diseases, respectively. As mentioned previously, PROG also attenuates glutamate excitotoxicity through conversion to ALLO and subsequent activation of $GABA_A$ and σ1 receptors [13,15].

These mechanisms—reduced inflammation and lipid peroxidation, maintenance of BBB integrity, and ionic stability–all serve to reduce edema after TBI [233,236] and stroke [8,52,130]. Recent findings also indicate that PROG can regulate expression of aquaporin-4 (AQP4), the water channel present in astrocyte endfeet and thought to be important in edema formation [107]. Since brain swelling is one of the main neurological causes of mortality after TBI, this is an important issue in the clinical management of brain-injured patients.

Both the ProTECT trial [300] and that reported by Xiao et al. [302] demonstrated improved functional recovery for patients receiving PROG after TBI. This is an important issue because ultimately the test of a pharmacological intervention is its effect on functional outcome and quality of life. In this context, PROG has shown improved long-term recovery in a number of behavioral paradigms including cognitive, sensory, and spatial learning and memory [232]. These effects have been seen in different models of mild, moderate, and

severe experimental injury [21,244]. The ability to sustain the neuronal circuitry implicated in complex behaviors is an important component of recovery. As expected, PROG has also been shown to attenuate retrograde neuronal degeneration in the nucleus basalis of Meynert (NBM) [114] and to maintain ACh homeostasis by regulating choline acetyltransferase (ChAT) levels in both TBI [63] and spinal cord injury [149]. In addition to affecting connectivity, PROG also helps in signal transmission by promoting myelination and remyelination of injured neurons, and maintaining myelin basic protein (MBP) at control levels [148]. MBP levels are associated with the establishment of a glial scar. These facts suggest that rather than just stopping further damage, PROG in fact initiates repair mechanisms [148,150].

3. Vitamin D and Neuroprotection

The term “Vitamin D” is something of a misnomer. Although the name is still in use for popular and historical reasons, vitamin D is more properly classed as a secosteroid because it consists of a cholesterol backbone and exerts steroid-like effects throughout the body, directly affecting the expression of over 1,000 genes [70] through the nuclear steroid vitamin D receptor (VDR). It has been shown to affect systems similar to those modulated by other hormones and steroids [89], with which it may interact in a variety of physio-pathological contexts [165,171,250,251,294]. Vitamin D is also a neuroactive steroid, because both the final activating enzyme and its nuclear receptor are known to be widely distributed throughout the CNS [89].

Vitamin D's physiological role was long believed to be limited to Ca^{2+} and phosphate homeostasis and the formation and maintenance of bone [58,59,89,117,122,306]. Recent evidence, however, suggests a much wider role for this compound, especially in its biologically active form, which includes modulation of the immune system [31,59,100,113,117,122,172], the renin-angiotensin system [227], development of cardiovascular disease [176,186], neuromuscular function [222], cell cycle control [9,310], and cancer [220].

3.1. Vitamin D Deficiency and its Consequences

According to the Third National Health and Nutrition Examination Survey, 61% of Caucasian- and 91% of African-Americans are D-deficient [139]. Similar figures have been cited for all segments of the population and in many countries [75,124,169]. Although D-deficiency is common in healthy young populations in industrialized nations [58,89,122,306], it is especially frequent in the elderly, especially in resident (nursing) homes and patients with hip fracture [163], with reported prevalence ranging from 65% to 74% in hospital inpatients [38,50,269], to 87% in elderly institutionalized patients [153] and 86% in institutionalized postmenopausal women [90]. It is a significant problem that has been called the “silent epidemic” [118], with a number of potential consequences, many of which are still unknown.

Vitamin D levels are commonly determined by serum levels of 25-hydroxyvitamin D_3 ($25OHD_3$), with levels below 25nmol/L defined as deficiency, levels between 25nmol/L and 50nmol/L defined as insufficiency, and higher than 50nmol/L as normal [164], although exact cutoff values are still being debated [121,124]. Levels below 20nmol/L are associated with rickets and adult osteomalacia, the hallmark of deficiency, but recently the value range considered necessary for optimal health has shifted to 100-120nmol/L [223], and a daily intake of at least 2000 IU/day has been suggested [58].

Aside from its classical effects on bone density, D-deficiency has been associated with a number of systemic conditions such as secondary hyperparathyroidism [120,181], metabolic

syndrome [220], hypertension [159,289], obesity [226], and diabetes mellitus [93,99], as well as cardiovascular disease events such as stroke and congestive heart failure [189,285], all of which can significantly affect a patient's ability to recover from severe trauma. Several recent studies also suggest that inadequate vitamin D may predispose towards Parkinson's and other neurodegenerative diseases [72], mood disorders [89,134], and even tuberculosis infection [308].

The relationship of vitamin D to autoimmune disorders is especially relevant to diseases of the CNS, and deficiency has been associated with increased incidence of multiple sclerosis (MS) [27,29,99], Sjögren's syndrome [132], rheumatoid arthritis [2], and Crohn's disease [127,215,216]. Systemic vitamin D levels have been suggested as a possible explanation for the latitudinal gradient in MS incidence (nearly zero at the equator and increasing with greater distance from it) [204], and correlations have been observed between circulating vitamin D status and the risk of developing MS [27,278], as well as a protective effect of vitamin D intake in both human disease [195,249] and animal models [28,88,156]. Vitamin D therapy for MS has been shown to be safe in humans [141] and has recently been recommended for use in double blind controlled clinical trials [204,248].

A low level of vitamin D is also one of the key markers of frailty, defined as a “global impairment of physiological reserves involving multiple organ systems” [274]. Frailty often results in a reduced capacity to maintain physical and psychosocial homeostasis and greater vulnerability to internal and environmental stressors such as trauma [175,274]. This could be especially important in the elderly, who are already more vulnerable to TBI, and studies have shown that advanced age is a major predictor of injury severity after TBI [194]. Other potentially exacerbating factors in the aged include systemic issues such as kidney disease, hypertension, atherosclerosis and cardiovascular disease, diabetes, cancer, and hormonal imbalances such as hyperparathyroidism [212]. While all these conditions can independently affect responses to injury, each has also been associated by a growing literature with insufficient serum levels of vitamin D as a key and often ignored underlying problem [99,124,220]. Vitamin D status has been specifically associated with functional outcomes in the elderly [18,55], suggesting that supplementation could be especially helpful for this segment of the population [55].

3.2. Vitamin D Synthesis, Activation, and Metabolism

The first step in the synthesis of VDH is the activation in the epidermis of 7-dehydrocholesterol by sunlight, specifically ultraviolet B (UVB) radiation in the 290-320nm range [108]. Because DNA absorbs UVB in exactly the same spectrum, vitamin D is hypothesized to have evolved as a “sunscreen” for DNA [117]. This is supported by the fact that it is present in animals ranging from phytoplankton to humans [117]. The UVB radiation opens the B ring of the steroid precursor, resulting in the conjugated triene system that characterizes all D vitamins and defines them as secosteroids [67,207]. Although seven forms of vitamin D exist, D_3 is the naturally occurring form in animals and is present in the skin of all higher vertebrates [207].

After its activation by sunlight, vitamin D is activated to VDH in two enzymatic steps. The first of these occurs in the liver by the cytochrome P450 enzyme, vitamin D 25-hydroxylase (CYP2R1) [122]. This step is not tightly regulated and therefore the product, $25OHD_3$, is a good indicator of overall vitamin D status [207]. The second step requires the 25-hydroxyvitamin D_3 1α-hydroxylase enzyme (CYP27 or 1α-OHase) and is a tightly controlled reaction regulated primarily by VDH itself, but also by levels of parathyroid hormone (PTH), calcium, and phosphate [67]. 1α-OHase is most abundant in the kidneys, although recent evidence has shown that it is present throughout the body, including the immune system [113,268,277] and the rodent and human brain

[7,73,74,94,[116],[152],[183],261,262,275,286]. The ubiquitous distribution of 1α-OHase suggests that VDH has both local and systemic effects (due to its synthesis by the kidneys and release into the bloodstream), and recent research suggests that a significant percentage of all VDH activity is autocrine or paracrine [163]. VDH is inactivated by 25-dihydroxyvitamin D_3 24-hydroxylase (CYP24), which is present in almost all VDH target cells, is induced by VDH, and is regulated in a manner reciprocal to 1α-hydroxylase, allowing for very tight local and global control of VDH levels [67]. The fact that the CNS can locally catalyze both its activation and inactivation makes VDH by definition a neurosteroid [89].

Vitamin D and its metabolites are largely bound in the blood by vitamin D binding protein (DBP), also known as group-specific component of serum or Gc-globulin. DBP serves as the main reservoir and transporter of the vitamin D endocrine system, and binds about 88% of the total $25OHD_3$ and 85% of the total VDH in serum [207]. This is an important fact in the pharmacokinetics of VDH, since only the free concentration of the hormone is considered to have biological activity [296]. Only about 5% of DBP is bound to vitamin D metabolites, and its serum concentration is about 20-fold that of the various vitamin D species [296]. DBP is an acute phase protein produced by the liver, and is upregulated by estrogen and during pregnancy when PROG is also very elevated [207].

3.3. Vitamin D Signaling Mechanisms

Most action of VDH is mediated by the VDR, a ligand-inducible transcription factor that regulates gene expression by binding to specific vitamin D response elements (VDREs) in DNA [39,43,59,110,265,290]. The specificity of the receptor for VDH is some 100 - 1000 times higher than for its precursor $25OHD_3$ [207]. Like other nuclear steroid receptors, the ligand-receptor complex effects gene transcription after undergoing heterodimerization with the retinoid X receptor (RXR) and recruitment of nuclear receptor coactivation proteins [22,43,59,177,197,217,265,270]. The VDR belongs generally to the protein superfamily that includes receptors for PROG, estrogen, glucocorticoids, androgens, thyroid hormone, and peroxisome proliferator-activator receptor (PPAR) [207] and more specifically to the NR1I subfamily of orphan nuclear receptors, which also includes the PXR and the constitutive androstane receptor (CAR) [228]. It is interesting to highlight here that the VDR is closely related (60% homology in the DNA-binding domain) to the PXR, a xenobiotic sensor through the activation of which PROG may exert some of its neuroprotective effects [144,151,217]. This suggests potential interactions and cross-talk between the two systems.

VDRs are widely distributed throughout the embryonic and adult brain, and appear most prominently in the neuroepithelium and proliferating zones in both rats [152,263,265,282,286] and humans [74]. Their presence has also been noted in neurons and glia of the human prefrontal and cingulate cortices, thalamus, hypothalamus, cerebellum, substantia nigra, caudate, putamen, amygdala, and hippocampus [24,74], although notably not in the macrocellular cells within the NBM and the septum [74]. This distribution is mostly coextensive with the presence of 1α-OHase, except in the NBM, where 1α-OHase was present but VDR was not [74]. This expression largely coincides with VDR and 1α-OHase distribution in the rodent brain [24,74], and also strongly overlaps with the known distributions of receptors for androgens, glucocorticoids, estradiol, and PROG [46,81,137,224]. There is also significant overlap between VDR and 1α-OHase expression in the brain, and VDH synthetic and degradative pathways have been described in neurons and glia [47,201-203,309]. This implies that VDRs in the brain are very likely activated by locally synthesized VDH and suggests a functional role for the hormone in the CNS [24].

Like most steroid hormones, VDH is also capable of rapid, non-genomic signaling [67]. These responses are likely mediated by receptors located on the cell surface, and although it has been suggested that these rapid events modulate genomic activity of VDH, the exact

function of this signaling pathway has not yet been determined. Although previously thought to be a different receptor protein, the VDH receptor involved in non-genomic signaling now appears to be the VDR, but in this case it is located not in the nucleus or cytosol but rather in membrane caveolae [207]. These caveolae, or lipid rafts, are invaginations in the plasma membrane and believed to be involved in the signal transduction of a number of signaling systems [5]. These rapid effects include activation of phosphoinositide metabolism [17,192], cyclic guanosine monophosphate (GMP) [106,284], protein kinase C (PKC) [266], MAPKs [14,252], opening of Cl^- channels [307], and stimulation of cellular Ca^{2+} levels [160,167,192,264].

3.4. Vitamin D as a Neuroprotective Agent

3.4.1. *In vivo* models—VDH treatment has shown promising results in a variety of *in vivo* and *in vitro* CNS injury paradigms. In a model of stroke, Wang and colleagues showed that VDH pre-treatment for 8 days can significantly increase levels of glial-derived neurotrophic factor (GDNF) and attenuate cortical infarction induced by middle cerebral artery (MCA) ligation in rats [291]. In various modes of Parkinson's disease, a number of researchers have shown that 7 – 8 day pretreatment with VDH can restore levels of dopamine in the substantia nigra of 6-hydroxydopamine lesioned rats [287] and prevent lipid peroxidation and cytosolic cytochrome c in zinc chloride-infused rat substantia nigra [162]. VDH pretreatment also prevented iron-induced oxidative injuries in the locus coeruleus (LC) of the rat [41]. Although these studies used a preventive paradigm by administering VDH for up to 8 days prior to injury, other studies have shown post-injury treatment benefits of VDH as well. Oermann and colleagues found that treatment with VDH after a photothrombotic lesion to the cerebral cortex of rats reduces the expression of glial fibrillary acid protein (GFAP), a key marker of reactive gliosis, in remote areas of secondary damage [209]. One recent report by Chabas and colleagues [34] examined axon regeneration after peripheral (peroneal) nerve injury in rats followed by chronic treatment with vitamin D2. The authors reported that the treatments enhanced the formation of new axons as well as increasing axon diameter and improving sensory responses to metabolic stimulation.

Further research has shown that concurrent administration of VDH with lipopolysaccharide (LPS) significantly inhibited inducible nitric oxide synthase (iNOS) expression in monocytes in the rat brain, suggesting that VDH can also help attenuate immune-induced oxidative damage in the CNS [86]. Lin et al. found a similar effect on zinc-induced toxicity in the CNS, where concurrent administration of VDH reduced apoptosis and oxidative damage [161]. VDH was also found to perform a direct anti-convulsant role in the brains of mice with chemically induced seizures [135].

The majority of *in vivo* studies with VDH, however, have focused on its effect on MS and its animal model, chronic relapsing EAE. The VDH effect in this model has been known for a long time [89,156]. VDH has been reported to be able to block the development of disease after onset in both rats [198] and mice [28], an improvement correlated with inhibition of iNOS [84,88], CD4 antigen expression [198], and IL-12-dependent T_H1 cell development in the CNS [179]. VDH also increased levels of transforming growth factor β (TGFβ) and IL-4, which were increased in a mouse model and are anti-inflammatory T_H2 immune response cytokines [30]. In another EAE system, VDH significantly reduced acute inflammation and levels of GFAP by inducing inflammatory cell apoptosis [253]. Since a significant component of secondary damage after many types of brain injury including TBI is related to excessive and prolonged inflammation, these data suggest that VDH might be an effective adjunct to treatments for immune disorders of the CNS.

3.4.2. *In vitro* models—There is also significant *in vitro* evidence for VDH neuroprotection. Two studies using mesencephalic dopaminergic neuron culture have shown that VDH protects these neurons from glutamate and dopaminergic toxins by increasing neuronal functions that serve to reduce oxidative stress [125,245]. A similar anti-oxidant effect was described by Garcion et al., who found that VDH treatment increased γ-glutamyl transpeptidase (γ-GT) expression and activity, enhanced glutathione pools, and reduced nitrite production in LPS-stimulated primary rat astrocyte culture [85]. In addition to anti-oxidant activity, VDH has been observed to reduce the production of inflammatory cytokines TNFα, IL-6, and nitric oxide (NO) in stimulated microglia [155]. In addition to neurons, astrocytes, and microglia, VDH has an effect on oligodendrocytes [7] and Schwann cells [51]. VDH also appears to regulate the expression of N-myc, c-myc, PKC, and TGFβ in neuroblastoma cells [283], suggesting that it may affect neural cell growth in ways other than the well-established induction of NGF and its receptors [23,51,202,237,238,297].

In addition to NGF, VDH can directly affect the expression of other factors involved in regeneration and recovery after CNS injury, including GDNF [199], neurotrophin 4 (NT-4) [201], and insulin-like growth factor binding proteins (IGFBPs) [177]. The results from these studies suggest that not only does VDH affect oxidative stress, neurotoxicity, oxidative stress, and growth factor expression, but it also works on all cell types involved in the development of and recovery from CNS injury including neurons, astrocytes, oligodendrocytes, and immune cells such as monocytes and microglia.

3.5. Vitamin D Mechanisms of Action

The primary non-calcemic effect of VDH appears to be inhibition of cell proliferation and stimulation of cell differentiation, especially in the immune system, where it acts as a powerful modulator [31,43,59,101,[112],117,122,172,296]. VDH has been shown to skew all aspects of immune function (T-cell differentiation, macrophage and dendritic cell maturation and antigen-presenting ability, cytokine profiles) towards a type 2 immune response, which is generally anti-inflammatory and regulatory.

This pro-inflammatory versus anti-inflammatory dynamic seems to be an important factor in the development of extended and damaging inflammation and in the genesis of the most likely cause of death for TBI victims, multi-organ system (MOS) dysfunction and failure [154]. Naïve, or T_H0, $CD4^+$ cells can differentiate into one of two phenotypes: in the presence of Interleukin-12 (IL-12) they develop pro-inflammatory T_H1 characteristics, which consist of production and release of TNF and Interferon-γ (IFNγ), further attraction of macrophages and monocytes, and activation of cell-mediated immunity and inflammation; in the presence of Interleukin-4 (IL-4), T_H0 cells develop an anti-inflammatory T_H2 phenotype, characterized by further production of IL-4 as well as Interleukin-5 (IL-5) and Interleukin-13 (IL-13), binding to B cells, and activation of antibody-mediated immunity [60,140,211,267]. These two general phenotypes mutually inhibit each other. This T_H differentiation appears to be of fundamental importance in the development of pathological inflammation in the hours and days after injury as the damaged system attempts to establish a dynamic equilibrium between the T_H1 and T_H2 populations and pro- and anti-inflammatory activity. This balancing act has consequences not only on the local injury environment, but on the organism as a whole. [138].

Like PROG, VDH has been shown to decrease levels of pro-inflammatory T_H1 cytokines such as TNFα, IL-1β, IL-12, IL-6, IFNγ [48,126,168,172,268,311], as well as the downstream reactive oxygen species generated by activated macrophages [133]. Long-term vitamin D deficiency has been shown to lead to generalized inflammatory conditions that compromise the cardiovascular system and glucose metabolism [119,123,157,208,292], the health of which is essential to survival post-TBI. In acute injury, chronic D-deficiency leads

to a more intense pro-inflammatory type 1 reaction, which could exacerbate the processes of damage secondary to the initial traumatic insult. Related to macrophage and microglial activity and T_H1 response is the production of reactive species that cause oxidative stress and contribute to secondary injury [19]. By modulating the development of a hyperactive and prolonged inflammatory response through adjusting T_H1/T_H2 balance and inducing macrophage apoptosis, VDH may limit the secondary injury cascade after TBI. This could be especially important under conditions of D-deficiency, where the underlying physiological state is already skewed towards a type 1 response [126,172,178,179,273].

Considerable evidence also exists for a direct modulatory effect of VDH on inflammation. VDH is known to down-regulate NFκB [54], the central mediator of inflammation that has also been linked with stress-response in humans [16] and stress-induced neuronal loss in rats [170]. VDH has also been shown to decrease inflammatory cytokine production in a variety of cell types, including endothelial cells [71], keratinocytes [109], monocytes [260], and microglia [155]. Systemic VDH administration has also been noted to lead to lower serum concentrations of TNFα and increased levels of anti-inflammatory IL-10 in heart failure patients [242], as well as lower TNFα and symptom manifestation in a rat model of inflammatory bowel disease (IBD) [311]. Finally, higher pro-inflammatory cytokine levels were found in VDR-KO (knock-out) mice [80], and an inverse correlation was seen between systemic inflammatory markers and $25OHD_3$ levels [271].

Since increased cellular Ca^{2+} concentration is the final common step in the initiation of cell death after injury, maintenance of adequate intracellular levels of Ca^{2+} is important for cell health and survival, not just in neurons but also in astrocytes and oligodendrocytes. VDH helps to regulate these levels and the cellular response through several mechanisms: 1) maintenance of adequate systemic parathyroid hormone (PTH) levels, 2) regulation of L-type voltage-sensitive Ca^{2+} channel (L-VSCC) expression, and 3) control of intracellular Ca^{2+} buffering systems. Control of systemic Ca^{2+} metabolism, along with regulation of parathyroid activity and PTH levels, belongs to the classical set of vitamin D functions; a state of D-deficiency can lead to increased PTH secretion, which in turn leads to increased intracellular Ca^{2+} concentrations that can increase the likelihood of Ca^{2+} overload and cell death in case of severe injury. In addition, and very importantly for amelioration of secondary injury after trauma, VDH has been observed to be neuroprotective in primary rat hippocampal cultures through the inhibition of L-VSCCs, which are strongly implicated in the development of glutamate-induced excitotoxic injury [20]. Finally, VDH upregulates proteins of the intracellular Ca^{2+} buffering system such as calbindin-D28k and parvalbumin [147,304], thereby improving the ability of cells to cope with increased intracellular Ca^{2+} levels without entering the irreversible path towards cell death. The general effect of these mechanisms is enhanced resistance to perturbations and improved cellular adaptation. A vitamin D-deficient state, however, can lead to increased susceptibility to Ca^{2+}-induced damage [42,57,220].

VDH is also a powerful regulator of the cell cycle: it inhibits cell proliferation and stimulates cell differentiation, and it is most likely this ability to control the cell cycle that makes it effective as an anti-inflammatory and an anti-neoplastic agent [9,109,136]. On a molecular level, several different microarray analyses indicate that VDH has effects on cell cycle regulating genes such as p53, $p21^{CIP1/WAF1}$, $p27^{KIP1}$, which are involved in apoptosis and control of the G_1/S phase transition [128,131], and growth arrest and DNA-damage-inducible, alpha (GADD45), which is involved in the G_2/M phase transition [69,70,100,290,295]. VDH may control other aspects of the cellular reproductive machinery such as various cyclins and cyclin-dependent kinases [39,129]. Since terminally differentiated neurons undergoing severe stress are known to re-enter the cell cycle, only to be forced to undergo apoptosis because they have lost their ability to proliferate

[32,61,79,145,184,310], the ability of VDH to induce cell cycle arrest and DNA repair might also be neuroprotective after TBI. Several studies suggest that this may be the case, and inhibition of cell cycle reentry has been neuroprotective in both experimental TBI [62] and Alzheimer's disease [200] models. Since a significant amount of the damage in TBI is caused by a secondary cascade of injury mechanisms [256,257], maintaining G_0 phase neurons in that state and inducing p53-mediated DNA repair could be a way to reduce post-TBI cell death and improve long-term neuronal survival [145].

4. Why Combine Vitamin D and Progesterone?

4.1. Potential interactions with other neurosteroids, especially PROG

There is growing evidence that vitamin D may interact with other neurosteroids such as PROG and estradiol in a variety of tissues. For example, VDH has been found to stimulate estradiol and PROG secretion in human placenta [10], and it is known to interact with PROG and estrogen in maintaining bone health, especially in post-menopausal women [90,119]. VDR gene polymorphisms have also been associated with breast and prostate cancer risk [166,230], suggesting not only that there may be crosstalk among the different steroid signaling pathways, but also that the hormonal context within which a single compound operates may modulate the end effect. Especially intriguing is the finding that xenobiotic activation of the PXR (for which PROG is a ligand and by way of which it may exert some of its neuroprotective effects [11,151]) can lead to drug-induced osteomalacia by upregulating the expression of CYP24 [218,303], the chief metabolizing enzyme of VDH. Furthermore, we have also observed that TBI induces lower serum levels of $25OHD_3$ (unpublished observation), suggesting that injury itself may cause a vitamin D-insufficient state. Given that PROG is a promising treatment for TBI that has been shown to work in a number of model systems and in human patients [258,259], the possibility that it may interact with vitamin D could have important consequences for treatment outcomes, and opens the possibility of developing a combined TBI treatment that may not only overcome the effects of vitamin D deficiency in the human population but may also enhance the effects of PROG treatment in normal patients with TBI.

From our review of the literature it is growing more apparent that vitamin D and PROG affect many of the same as well as a number of divergent processes involved in the repair of secondary injury following TBI. The similarities may be explained by the fact that VDRs have been found in rodent (and human) microglia, astrocytes, oligodendrocytes and Schwann cells [180], which are known to play a role in inflammation and CNS repair and which are also directly affected by PROG treatment after CNS injuries. It is certainly possible that, if PROG and VDH each work through different pathways to reduce cellular injury and enhance the metabolic processes of repair, then a combination of these agents might lead to more rapid neuronal repair and functional recovery, perhaps even with less dosing and duration of treatment.

A reason to attack the same injury pathways with different compounds lies in the fact that the same repair mechanisms may be modulated through different signals. An example of this would be intracellular Ca^{2+} levels, which can be independently affected by the reduction of glutamate excitation and by intracellular buffering systems. Here, a combination of PROG's actions through the GABAergic system to inhibit extracellular activity and the action of VDH to increase intracellular Ca^{2+}-binding proteins would both have an effect on calcium metabolism, but via different sub-pathways [239]. Another example would be apoptosis, which may be reduced by a number of different mechanisms: effects on Ca^{2+} metabolism, induction of trophic factors, inhibition of inflammation and pro-apoptotic signaling, and/or a reduction in lipid peroxidation by reactive species. Two different compounds that affect the

same mechanism in this case would be synergistic and presumably enhance the protective effect after a CNS injury.

Another rationale for using a drug combination that affects the same mechanisms is the well-known inverted U-shaped dose response (or hormesis) of steroid action [25,49], in which the optimal result is obtained with a medium-range dosage while increasing dosages decrease the effectiveness. Why hormesis occurs is not clear, although recent mathematical modeling studies suggest that the artifact may be due to the second-order steroid receptor kinetics that produce a parabolic dose response curve [158]. If the kinetics of the receptor mechanism indeed impose a limit on steroid action, it may be beneficial to attempt to overcome individual system saturation and activate similar protective end mechanisms through different steroid pathways [288,293]. As an example, PROG and VDH may increase the activity of γ-GT by different mechanisms (PR-PROG activity and VDR-VDH activity), resulting in an increased overall antioxidant capacity. Although this is still not fully confirmed, the suggestion that it may be possible to amplify a neuroprotective effect simply through drug combination is intriguing and worth further exploration.

This concept can be extended to fully divergent mechanisms if one assumes that fewer damaging processes are ultimately better for protection and recovery. A complication may arise here if certain processes, such as inflammation [36], are potentially beneficial in the short term but end up being detrimental in the longer term, in which case an optimal treatment would only be achieved through the use of multiple agents given at different time points in the injury cascade. Another complication may involve non-linear interactions between PROG and VDH such that what may be best doses for treatment with each individually may not work optimally in combination. Some of our initial data (unpublished observations) indeed suggests that this may be the case. This means that dosing parameters may have to be specifically reconfigured for novel combination therapies. Regardless of such considerations, a recent NINDS Workshop on Combination Therapies specifically recommended that, “With its [PROG's] pleiotropic characteristics, it would be advantageous to consider combination therapies for TBI that combine PROG with other agents that 1) protect the intracerebral vasculature, 2) diminish the effects of glutamate release and calcium influx, 3) more directly protect the mitochondria, 4) protect against the toxic effects of heme breakdown products, 5) enhance free radical scavenging, 6) enhance cerebral blood flow, 7) modulate the kalkrein-kinin system, 8) protect the axonal and cytoskeleton infrastructure, and 9) protect against diffuse axonal injury” [174]. VDH meets several of these recommendations for a combinatorial agent:

1. **1.** Diminish the effects of glutamate release and calcium influx:

   VDH maintains intracellular Ca^{2+} through downregulating L-VSCCs and upregulating intracellular Ca^{2+} buffering capacity [57,147,304].

2. **2.** Protect against the toxic effects of heme breakdown products:

   VDH has been reported to upregulate glial heme oxygenase-1 (HO-1) concomitantly with a reduction in GFAP following focal cortical ischemia [209]. HO-1 is one of the rapidly induced heat shock proteins which metabolizes and thus detoxifies free heme to the powerful endogenous antixodants biliverdin, CO and Fe2+ [173,182]. These studies suggest that HO-1 induction by VDH protects cells from the oxidative toxicity of free heme.

3. **3.** Enhance free radical scavenging:

   VDH induces the expression of γ-GT and significantly increases intracellular glutathione in response to LPS-induced oxidative stress in astrocytes [85] and protects neurons from chemical toxicity [245].

4. Modulate the renin-angiotensin system:

   VDH plays an important role in the regulation of renin biosynthesis and blood pressure homeostasis [143]. It also functions as an endocrine suppressor of renin biosynthesis and genetic disruption of the VDR results in overstimulation of the renin-angiotensin system (RAS), leading to high blood pressure and cardiac hypertrophy [301].

5. Protect the axonal and cytoskeleton infrastructure:

   VDH potentiates axon regeneration in a rat model of peripheral nerve injury [35]. Following nerve injury, treatment with vitamin D_2 (100 IU/kg/day) significantly increased axogenesis and axon diameter, improved the response of sensory neurons to metabolites such as KCl and lactic acid, and induced a fast-to-slow fiber type transmission of the *Tibialis anterior* muscle.

It therefore seems clear that VDH not only shares many CNS repair mechanisms with PROG, but also adds to the mechanisms of action that compensate for missing mechanisms in PROG's arsenal.

Finally, in the context of aging and vitamin D deficiency, it makes sense to assume that whatever damage or exacerbation caused by D-deficiency can be at least partially overcome with supplementation to correct the deficiency. To this end, and since we are primarily interested in developing and improving treatment modalities, we recommend that treatment be combined with VDH to correct the potential loss of efficacy of PROG treatment in the D-deficient aged population. If this is effective, it could have significant implications for the treatment of elderly people with TBI.

5. Conclusion

Insults to the CNS, including TBI, induce neuroinflammatory and oxidative stress reactions, which then induce the secondary cascade of brain damage. As noted in this review, both PROG and VDH are pleiotropic hormones acting on several common, as well as on independent, CNS pathway mechanisms to reduce CNS damage and enhance CNS repair after TBI. Many studies now show that treatment with PROG significantly improves functional outcome after TBI in rats and humans [91,246,254]. PROG has been shown to reduce inflammatory responses [53,115,214] and oxidative stress. In addition PROG can activate protective pathways and increase the expression of genes and proteins associated with neuroprotection after brain damage. VDH has also been reported to be neuroprotective in a variety of *in vitro* and *in vivo* models including cortical infarction [291], zinc-induced neurotoxicity [162], EAE [87], LPS-induced oxidative stress [85] and Parkinson's disease [245,287]. VDH has an immunomodulatory effect and regulates the differentiation, growth and function of a broad range of immune system cells [1]. A growing literature demonstrates that VDH restriction impairs a number of physiologic processes associated with healthy CNS functions such as mitosis, mitogenesis, neurite outgrowth, possibly adult neurogenesis in hippocampal cells, and mitochondrial dysfunction [4]. Treatment with VDH induces the expression of NGF, GDNF, pro-apoptotic proteins [142] and upregulation of OH-1 and reduction in GFAP immunoreactivity in injured brain [209]. Given the wide spectrum of action by the two hormones it is likely that a combination of the two, operating through unique and slightly different but compatible molecular mechanisms, might be synergistic in reducing the cytotoxic events associated with the injury cascade and increasing the neuroprotective events related to anti-apoptotic signaling and brain repair.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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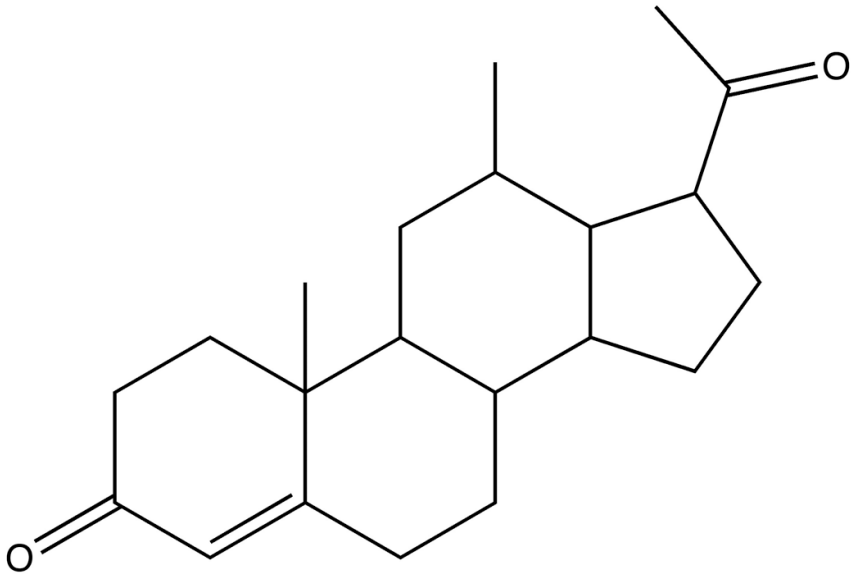

Figure 1. Progesterone
The chemical structure of progesterone.

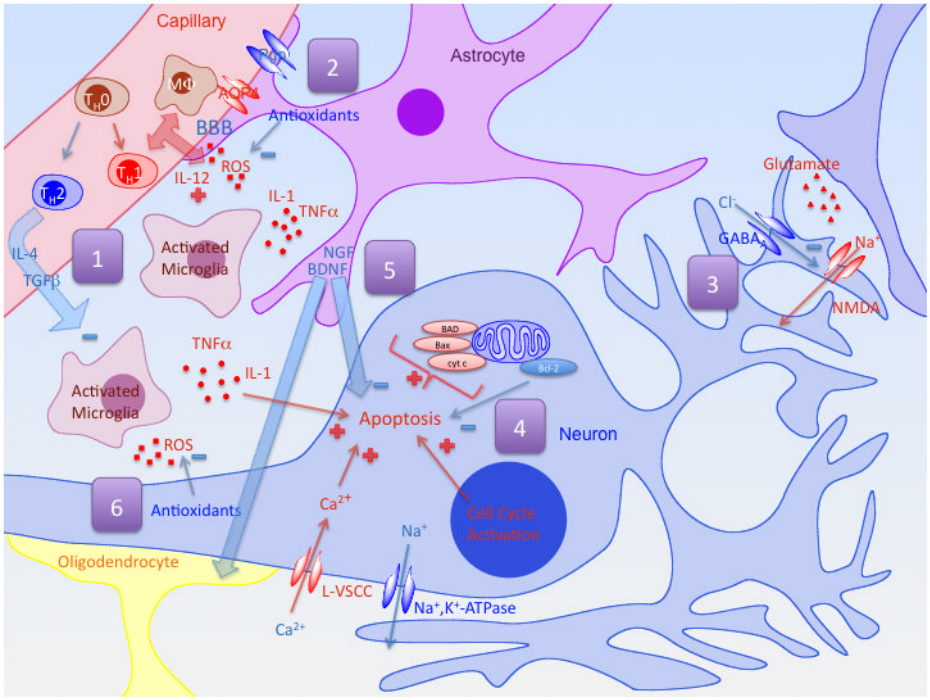

Figure 2. Brain injury processes affected by PROG and VDH

Both PROG and VDH are pleiotropic and affect multiple pathways, which may account for their therapeutic effectiveness. Here we show a few of the major pathways involved in injury and discussed in this paper, with the general scheme of blue as beneficial or protective and red as detrimental. 1. Inflammatory pathways consisting of immune cell recruitment and infiltration (macrophages; MΦ), microglial activation and inflammatory cytokine release (TNFα and IL-1), and naive T cell (T_H0) differentiation into pro-inflammatory type 1 (T_H1) and anti-inflammatory type 2 (T_H2). These processes can lead to cell death, edema, and secondary damage; 2. Maintenance of blood-brain barrier (BBB) integrity, including modulation of the expression of channels and transporters such as P-glycoprotein (Pgp) and aquaporin 4 (AQP4) and antioxidant protection for both capillary endothelium and astrocytes. Failure of BBB function is a key component in the development of edema; 3. Glutamate excitotoxicity, mediated primarily by NMDA channels, can be toxic to the cell due to Na+ influx and severe depolarization. These effects can be counteracted by Cl^- influx through $GABA_A$ channels, leading to repolarization; 4. The balance of cellular pro- and anti-death mechanisms, including release of pro-apoptotic mitochondrial (Bax, BAD, cytochrome c) and anti-apoptotic (Bcl-2) proteins, caspase-3 activation, maintenance of ionic and energy balance, as well as reduction of Ca^{2+} influx, which is the final common pathway of most mechanisms of cell death including glutamate toxicity. Since the activation of cellular reproductive machinery in terminally differentiated neurons can also lead to apoptosis, arrest of the cell cycle can also be protective; 5. Upregulation of trophic factors, especially NGF and BDNF, which contribute not only to the maintenance of neurons and astrocytes, but also oligodendrocytes and myelination; 6. Antioxidant defenses, which reduce the damage of immune and endogenously released reactive oxygen species (ROS) to cellular components and membranes. L-VSCC: L-type voltage-sensitive Ca^{2+} channel; Na^+,K^+-ATPase: Na^+/K^+ active transport pump.

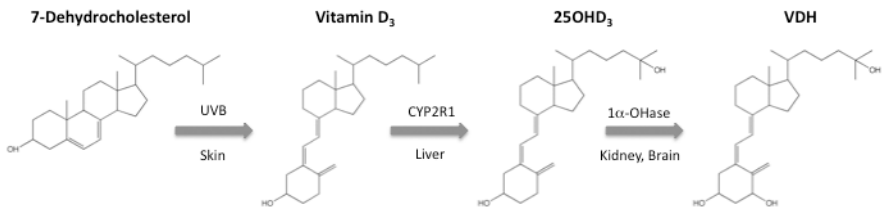

Figure 3. Metabolism of VDH

The metabolism of vitamin D and its conversion from 7-dehydrocholesterol to vitamin D hormone (VDH). $25OHD_3$: 25-hydroxyvitamin D_3; UVB: ultraviolet B solar radiation; CYP2R1: vitamin D 25-hydroxylase; 1α-OHase: 25-hydroxyvitamin D_3 1α-hydroxylase.

Table 1

Neuroprotective mechanisms of PROG and VDH.

MECHANISM	PROGESTERONE	VITAMIN D
NEURONAL APOPTOSIS	↓ cytochrome c [239] ↓ bad, bax [3,63,83,205,298,305] ↓ caspase-3 [3,63,83,205,298,305]	↓ cytochrome c [162] ↓ cell cycle (neurons) [9,109,136,310]
	↑ bcl-2 [3,63,83,205,298,305] □ mitochondrial function [56]	□ n-myc, c-myc [283]
TROPHIC FACTORS	↑ NGF [213,272]	↑↑ NGF [23,51,202,237,238,297]
	↑ BDNF [95,96,241]	↑ GDNF [199,291], NT-4 [201], TGFβ [283] □ IGFBPs [177]
INFLAMMATION	↓ GFAP [63,107] ↓ TNFα, IL-1 [66,114,190,221] ↓ NFκB [221] $T_H2 > T_H1$ [178]	↓ GFAP [209,253] ↓ TNFα, IL-1 [48,126,155,168,172,268,311] ↓ NFκB [54] $T_H2 \gg T_H1$ [30,126,178,179,273] (↑ IL-4, ↓ IL-12, IFNγ)
	↓ complement (C3, C5) [221,280] □ coagulation [281]	□ antigen-presenting cells [277] □ immune proliferation [126]
OXIDATIVE STRESS	↓ lipid peroxidation [191,235,244] ↓ iNOS, NO, nitrites [66] ↓ immune ROS [53] ↓ toxicity [26,98,205,210] (Fe, MPTP, β-amyloid) ↑ glutathione [21]	↓ lipid peroxidation [161,162] ↓ iNOS, NO, nitrites [84,86,88,155] ↓ immune ROS [133] ↓ toxicity [41,162,245,287] (Fe, Zn, 6-OH dopamine) ↑ glutathione [85]
	↓ MnSOD [21] ↑ SOD [191]	↑ HO-1 [207] ↑ γ-GT [85]
EXCITOTOXICITY/Ca^{2+}	↑ $GABA_A$ [13] □ σ1 receptor [15]	↓ L-VSCCs [20] ↑ Ca^{2+} buffering [147,304] (calbindin, parvalbumin)
MYELIN/AXONS	□ MBP [148,150] ↑ myelination [12,150] (oligodendrocytes/CNS) ↑ remyelination [150,243] (Schwann cells/PNS)	↑ axogenesis [34,35] ↑ axon diameter [34,35]
OTHER	□ AQP4 [107] □ Pgp (BBB function) [53] □ ChAT (NBM) [63,114,149] □ Na^+,K^+-ATPase [82,149,231] ↓ Edema [114]	□ Renin-angiotensin [143,227]

Notes: Identical mechanisms are identified by gray shading, while divergent mechanisms are white. In cases of a stronger response with reference to one mechanism, a double indicator is used (↑↑ versus ↑). ↑ = increases, ↓ = decreases, > = greater than skew or bias, □ = modulates. Superscript numbers in brackets indicate the references for each effect.