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Review

Proposing Bromo-epi-androsterone (BEA) for perioperative neurocognitive disorders with Interleukin-6 as a druggable target

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HIGHLIGHTS

- Cognitive decline following surgery is an increasing concern, particularly in the elderly.
- Inflammatory cytokines, interleukin-1 beta (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα), are elevated in PND.
- The cytokine, IL-6, is required and sufficient for PND.
- BEA, a synthetic analog of DHEA, is a potent immune modulator and reduces inflammatory cytokines.
- BEA is proposed for clinical trial in hip replacement surgery to see if it will benefit PND as measured by reduction in IL-6.

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ABSTRACT

Cognitive impairment following surgery is a significant complication, affecting multiple neurocognitive domains. The term "perioperative neurocognitive disorders" (PND) is recommended to encompass this entity. Individuals who develop PND are typically older and have increases in serum and brain pro-inflammatory cytokines notwithstanding the type of surgery undergone. Surgical trauma induces production of small biomolecules, damage-associated molecular patterns (DAMP), particularly the DAMP known as high molecular group box 1 protein (HMGB1). Mechanistically, peripheral surgical trauma promotes pro-inflammatory cytokines that stimulate central nervous system (CNS) inflammation by disrupting the blood-brain barrier (BBB) causing functional neuronal disruption that leads to PND. PND is strongly linked to elevations in serum and CNS pro-inflammatory cytokines interleukin-1 beta (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα); these cytokines cause further release of HMGB1 creating a positive feedback loop that amplifies the inflammatory response. The cytokine IL-6 is necessary and sufficient for PND. Dehydroepiandrosterone (DHEA) is a principal component of the steroid metabolome and is involved in immune homeostasis. DHEA has been shown to suppress expression of several pro-inflammatory cytokines by regulation of the NF-kB pathway. Bromo-epi-androsterone (BEA) is a potent synthetic analog of DHEA; unlike DHEA, it is non-androgenic, non-anabolic and is an effective modulator of immune dysregulation. In a randomized, placebo-controlled clinical trial, BEA effected significant and sustained decreases in IL-1β, TNFα and IL-6. This article presents BEA as a potential candidate for clinical trials targeting PND and further suggests the use of BEA in elective total hip arthroplasty as a well-documented surgical entity relevant to the management of PND.

1. Introduction

Perioperative neurocognitive disorders (PND) refer to a spectrum of cognitive impairments that occur around the time of surgery and include both acute and long-term cognitive decline. Perioperative neurocognitive disorders (PND) include postoperative delirium, delayed neurocognitive recovery (dNCR), and postoperative neurocognitive disorder (PNCD), which can occur within 7 days, 8 to 30 days, and 1 to

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12 months after anesthesia/surgery, respectively. [1]. The relationship between surgery and cognition has long been recognized [2]. The first reference to cognitive problems following surgery was published in 1887; entitled "Insanity following the use of anaesthetics in operations." [3]; and the first modern era article was published in 1955 entitled "Adverse cerebral effects of anaesthesia on old people" [4]. The incidence of PND across the variety of surgical procedures ranges from 7 % to 56 % [5,6]. Since the 1950's postoperative cognitive issues were a commonly recognized complication of cardiac surgery [4]. Several patients who had been on the cardio-pulmonary bypass pump during surgery experienced cognitive decline, memory problems, and other postoperative neurologic symptoms. These symptoms were known as postperfusion syndrome or, informally, as "pumphead," reflecting the idea that prolonged exposure on the pump was somehow responsible for the neurological effects [7,8].

It is now recognized that PND is a manifestation of the systemic inflammatory response syndrome (SIRS) [9] induced by the sterile trauma of surgery [10]; it rapidly spreads by a cascade of molecular and cellular signaling pathways within the innate immune system with the greatest risk factor being the age of the patient [11,12]. The fact that peripheral trauma induces central inflammation is manifest in this study where there was no significant difference in the effect of general or spinal anesthesia on postoperative delirium in elderly patients with hip fracture [13–15].

Current management of PND involves a combination of non-pharmacological and pharmacological interventions aimed at prevention and treatment. For example, one intiative utilizes trained volunteers who engage postoperative patients in activities such as range-of-motion exercises and cognitive stimulation to prevent functional and cognitive decline of older persons during hospitalization [16,17]. Moreover, cognitive prehabilitation, using preoperative cognitive training, strives to enhance cognitive reserve [18]; optimizing sleep and managing pain as disturbances in sleep and poorly managed pain can both contribute to PND [19]. Pharmacologic intervention for PND has consisted of anti-inflammatory agents targeting neuroinflammation for which there is insufficient evidence to demonstrated effectiveness [20,21] leaving a therapeutic gap in treatment options. PND results in longer hospitalization, poorer prognosis and higher mortality rates [22,23]; demographics suggest an ever-increasing number of surgeries in the elderly resulting in an escalating need for mitigation of this postoperative condition [24].

2. Alarmins – Damage-associated molecular patterns (DAMPs)

The trauma associated with major surgery generates alarmins that are a group of endogenous molecules released by stressed or damaged cells. Alarmins function normally within cells, typically involved in processes such as maintaining cellular structure and DNA repair. However, when released extracellularly due to cell stress or damage, they act as danger signals: damage or danger-associated molecular patterns (DAMPs) [25]. DAMPs play a crucial role in the early stages of the immune response by alerting the immune system of tissue damage or infection – in the case of infection they are called PAMPs – pathogen-associated molecular patterns [26].

The inflammatory responses to infection and sterile tissue injuries have different purposes; while the former protects the host from infection and can be coupled with the induction of adaptive immunity, the latter primarily serves to promote tissue repair [27]. While initially helpful, the protective inflammatory repair processes driven by innate immunity can become harmful. This can happen when a low-grade immune response is insufficient to eliminate the inflammatory trigger, leading to improper resolution of the insult and the onset of chronic inflammation. Moreover, this can also happen when the immune response is exaggerated and uncontrolled, often linked to an overproduction of DAMPs. This leads to acute systemic hyperinflammatory disorders, characterized by "collateral damage," or chronic and excessive repair processes [28].

Upon release, alarmins bind to pattern recognition receptors (PRRs) on immune cells, neutrophils, macrophages and dendritic cells, to activate and recruit these cells to the site of injury contributing to the initiation and amplification of inflammation [29]. This activation leads to the release of the classic triad of pro-inflammatory cytokines: tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) [30].

3. High mobility group box 1 (HMGB1)

"Danger Theory" in which the injured tissues were postulated to release intracellular molecules that activate the immune system [31] remained only a theory until High Mobility Group Box 1 (HMGB1) was established as a prototypic DAMP [32]. HMGB1 is a significant and well-studied DAMP; it is a nuclear protein found in almost all cell types and it is released during cell stress, injury, necrosis, or apoptosis. The interaction between HMGB1 and the inflammatory cytokines is central to the perpetuation of the inflammatory response. HMGB1 and TNF-α are involved in a feedback loop that amplifies the inflammatory response: TNF-α induces release of HMGB1 which stimulates immune cells to produce more TNF-α. IL-1β can also induce the release of HMGB1; similar to TNF-α, IL-1β is produced in response to HMGB1 signaling and the two can bind together protecting IL-1β from degradation and prolongs its inflammatory effects. Lastly, HMGB1 stimulates the production of IL-6 by macrophages and dendritic cells. Il-6 is a key cytokine in the acute phase of inflammation signals but HMGB1 sustains Il-6 production contributing to chronic inflammation [33–35].

4. Neuroinflammation and perioperative neurocognitive disorders

With PND, the surgically induced systemic inflammatory response disrupts the blood-brain barrier (BBB) [36]. The pro-inflammatory cytokine triad of TNF-α, IL-1β and IL-6, when released into the bloodstream, cross the BBB and perpetuate neuroinflammation [37,38]. Cyclooxygenase-2 (COX-2) plays a significant role in the disruption of the BBB in PND [39]. COX-2 is an enzyme that is typically upregulated in response to inflammation, and it is involved in the synthesis of pro-inflammatory prostaglandins, which can negatively impact BBB integrity [40]. The memory disturbances imparted by pro-inflammatory cytokines are due to inhibition of long-term potentiation (LTP) [41,42].

5. IL-6: Necessary and sufficient for perioperative neurocognitive disorders

Although IL-6 appears, at normal levels, to have an important role in neurocognitive health, its dysregulation leads to pathological effects [43]. Elevated serum IL-6 levels have been associated with poorer cognitive performance in healthy subjects [44,45]. IL-6 expression is primarily activated by IL-1β and TNFα [46]. IL-6 is both necessary and sufficient to produce PND [47,48]. When given systemically or via surgery-induced (DAMP) upregulation, IL-6 is capable of causing cognitive decline [48]. The CA1 region of the hippocampus is responsible for long-term potentiation, the neuro-biologic correlate for learning and memory [41]. Importantly, in a mouse model for PND, the tibial fracture aseptic trauma model, appropriate bone healing occurs when IL-6 is blocked [49].

6. DHEA

DHEA (dehydroepiandrosterone) and its sulfate form (DHEA-S) are the most prevalent steroids in the human metabolome. They play crucial roles in various physiological processes, including metabolism, immune function, and stress response [50]. DHEA production varies throughout life, peaking in early adulthood and then steadily declining. By the age

of 70–80, DHEAS levels typically drop to only 10–20 % of those found in young adults [51].

DHEA and cortisol have opposing hormonal effects, and maintaining a balance between their levels is vital for numerous physiological functions [40]. DHEA is often referred to as the "youth hormone" [52–54] while cortisol is commonly known as the "stress hormone" [55]. A lower ratio of DHEA to cortisol has been linked to various health issues, including stress, metabolic syndrome, immune dysfunction, increased susceptibility to infections, frailty, and higher all-cause mortality rates [56–59].

Although the adrenal glands are the primary source of these steroids, they are also produced locally in other tissues, such as primary lymphoid organs, intestines, gonads, skin, brain, and heart [56]. The age-related decline in the DHEA/cortisol ratio is associated with changes in the immune system characteristic of aging (immunosenescence) [60–62] and a paradoxical increase in inflammation (inflammaging) [63].

7. BEA – (16 alpha-bromoepiandrosterone)

BEA (16 alpha-bromoepiandrosterone) is a synthetic analog of DHEA that lacks DHEA's androgenic and estrogenic effects. One of DHEA's primary mechanisms is as a potent inhibitor of mammalian glucose-6-phosphate dehydrogenase (G6PDH), and in this regard, BEA is approximately 60 times more potent than DHEA [64]. BEA, previously known as HE2000, was developed over two decades ago as a treatment for various human infections. It has been used in nine clinical trials, treating 228 participants for conditions including HIV, malaria, and hepatitis [64–67]. In March 1999, the FDA granted BEA investigational new drug (IND) status for use against HIV/AIDS [68,69], for which it demonstrated efficacy [70].

BEA has been shown to limit non-productive inflammation [71] and, due to its broad immune support, has been proposed as a potential treatment for *Mycobacterium tuberculosis*, the world's most significant pathogen [72,73].

As with DHEA, BEA promotes a T1 immune response and helps rebalance the Th1/Th2 ratio, which naturally decreases with age [70]. This rebalancing offsets the consequences of a Th2 shift commonly observed in older individuals, including increased susceptibility to infections, reduced response to vaccines, and a higher incidence of autoimmune disorders [74–76].

BEA in the previous clinical trials was mostly given intramuscularly (IM). The oil-miscible BEA, given IM, resulted in injection site reactions including pain and induration that ranged from mild to moderate [65,70]. The formulation of BEA is now changed to be water-soluble which may circumvent or mitigate the injection site adverse reactions [77].

8. Trial of Bromoepiandrosterone for perioperative neurocognitive disorder in Total hip arthroplasty

The world Health Organization (WHO) designated 2021–30 as the decade of healthy aging to foster healthy aging and improve the lives of older people, their families, and communities [78]. Not surprisingly, age-related surgical intervention for age-related infirmity is an ascendant problem as discussed in the global burden of disease study of osteoarthritis [79].

By 2030, a projected 572,000 elective total hip arthroplasties (THA) will be performed annually in the United States, continuing as among the most accepted and effective surgical procedures to preserve the function of the joint and alleviate pain [80,81]. As such, a trial of BEA to mitigate PND in individuals undergoing THA is a practical pharma application with an at-risk PND demographic.

9. Primary outcomes for BEA in Total hip arthroplasty: IL-6 and trail making test B

While the classic triad of TNF-α, IL-1β and IL-6 have been used to monitor inflammation in PND, IL-6 is the singular reported cytokine to be both necessary and sufficient to produce the surgical phenotype; this happens whether a dose of IL-6 was given systemically or if the IL-6 was generated through surgically induced systemic inflammation pathways [48,82]. Preoperative IL-6 is higher in study participants who developed POD compared with those who do not [83]. Importantly, in patients with PND, the resolution of elevated IL-6 is associated with the return of normal cognitive function [84]; moreover, as previously noted in the animal model, the anti-inflammatory action of BEA did not impair healing [49].

Additional study parameters may include dosing strategies informed by prior trials that delineate the timeline and magnitude of IL-6 levels in postoperative blood and CSF.

The Trail Making Test (TMT—B) is one of the most used neuropsychological screening tests for brain dysfunction [85] and has long been used to evaluate deficits in cognitive processing speed and executive function [86]. TMT-B can be administered at bedside making it a valuable tool for postoperative cognitive evaluation [87].

10. Summary

A peripheral surgery-induced innate immune response in elderly and otherwise susceptible individuals, can trigger an IL-6-mediated inflammatory process in the hippocampus that results in memory impairment [88]. This article proposes an intervention with BEA to reduce surgical trauma induction of pro-inflammatory cytokines that trigger PND. For a trial, we advocate for hip replacement, a procedure that has a known incidence for PND of approximately 17 % [89]. Success in such a targeted, well-described, surgical disease entity may spur the trial of BEA in other disease entities having neuroinflammation as a defining attribute.

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CRediT authorship contribution statement

Coad Thomas Dow: Supervision, Conceptualization, Writing – review & editing, Writing – original draft. **Zade Kidess:** Formal analysis, Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Coad Thomas Dow reports article publishing charges was provided by Protibea Therapeutics. Coad Thomas Dow reports a relationship with Protibea Therapeutics that includes: employment. C. Thomas Dow serves as the Chief Medical Officer for Protibea Therapeutics. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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