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Is TNF a Link between Aging-Related Reproductive Endocrine Dyscrasia and Alzheimer's Disease?

Ian A. Clark^a and Craig S. Atwood^{b,c,d}

^aResearch School of Biology, Australian National University, Canberra, ACT 0200 Australia

^bGeriatric Research, Education and Clinical Center, Veterans Administration Hospital, Madison, WI 53705, USA

^cDepartment of Medicine, University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI 53705, USA

^dSchool of Exercise, Biomedical and Health Sciences, Edith Cowan University, Joondalup, WA 6027, Australia

Abstract

This commentary addresses a novel mechanism by which aging-related changes in reproductive hormones could mediate their action in the brain. It presents the evidence that dyotic endocrine signals modulate the expression of tumor necrosis factor (TNF) and related cytokines, and that these cytokines are a functionally important downstream link mediating neurodegeneration and dysfunction. This convergence of dyotic signalling on TNF-mediated degeneration and dysfunction has important implications for understanding the pathophysiology of AD, stroke, and traumatic brain disease, and also for the treatment of these diseases.

Age-related dysregulation of the hypothalamic-pituitary-gonadal (HPG) axis (endocrine dyscrasia) leads to dyotic signalling and the induction of neurodegenerative cascades within the brain (see [1–4] for reviews). Neurodegeneration induced by this aging-related endocrine dyscrasia is mediated via a number of cell cycle-related mechanisms, leading to alterations in the blood-brain barrier [5] and neuronal viability [6–10]. Cell cycle-related biochemical and pathological changes include altered tau phosphorylation and amyloid- β precursor protein (A β PP) metabolism, endoreduplication (polyploidy), mitochondrial biogenesis, upregulation of mitogenic signalling pathways and oxidative stress. All these well-described changes associated with pyramidal neuron autophagy/apoptosis in the Alzheimer's disease (AD) brain also are observed during the progression of neurons through the cell cycle [2; 11], and are indicative of an aberrant re-entry of post-mitotic neurons into the cell cycle.

Endocrine Dyscrasia and Alzheimer's Disease

Changes in the brain concentration of HPG axis hormones with age-related endocrine dyscrasia have been demonstrated to induce numerous biochemical, physiological and pathological changes within the brain [2; 11]. In this respect, two groups of hormones have been most closely examined, the gonadotropins and sex steroids. Evidence supporting the elevation in the concentrations of circulating gonadotropins in neurodegeneration is

Address Correspondence and Reprint Requests to: Ian A. Clark, Ph.D., Research School of Biology, Australian National University, Canberra, ACT 0200, Australia, Tel. 61 2 6125-4363, ian.clark@anu.edu.au Or, Craig S. Atwood, Ph.D., University of Wisconsin-Madison Medical School, Wm S. Middleton Memorial VA (GRECC 11G), 2500 Overlook Terrace, Madison, WI 53705, USA, Tel. 608 256-1901, Ext. 11664, csa@medicine.wisc.edu.

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evidenced by 1) total brain concentrations of amyloid- β (A β), the major component of amyloid plaques, are increased by luteinizing hormone (LH) and decreased by the anti-gonadotropin leuprolide acetate [12; 13], 2) ovariectomy, which increases circulating gonadotropins, increases brain A β load [14], 3) mice over-expressing A β PP but lacking a functional LH receptor (A β PPxLHR $^{-/-}$) show greatly reduced A β deposition in the brain [15], 4) elevated LH/hCG diminishes cognitive function [16; 17], 5) ovariectomy also diminishes cognitive function [14; 18; 19], 6) low LH levels in rodents enhance spatial memory and protect against memory loss [20; 16], 7) leuprolide acetate improves cognition in a murine A β PP transgenic model [13; 19], 8) a phase II clinical trial of leuprolide acetate (<http://clinicaltrials.gov/ct/show/nct00076440?order=1/46>) demonstrated cognitive stabilization in AD patients over 48 weeks, 9) patients treated with leuprolide acetate for prostate cancer have a 50% reduction in the incidence of AD [21; 22], and 10) these neurodegenerative and cognitive changes are supported by the age-related elevation in gonadotropins and by the increased plasma levels of follicle stimulating hormone (FSH) and LH in men and post-menopausal women with AD above those of age-matched cognitively normal individuals [23; 24].

Evidence supporting the loss of sex steroid signalling in mediating neurodegenerative-like changes is evidenced by findings that, 1) 17 β -estradiol (E $_2$) and testosterone have been shown to alter neuronal A β PP processing toward the non-amyloidogenic pathway in both mouse and human cell lines and primary cultures of rat, mouse, and human embryonic cerebrocortical neurons [25–28], 2) ovariectomy, which suppresses circulating levels of estrogens, also has been shown to increase total brain A β concentrations in guinea pigs [29] and A β PP transgenic mice (e.g. [30; 26; 31; 32]). Conversely, 17 β -estradiol treatment was shown to partially and totally reverse the effects of ovariectomy in guinea pigs [29] and A β PP transgenic mice (e.g. [30]), 3) the negative correlation between serum E $_2$ in women with AD [33]; the negative correlation between serum testosterone in men with AD [23; 34] 4) the improvement in cognition in women with AD treated with E $_2$ in 3 controlled [35–37] and 1 uncontrolled [38] intervention studies; 5) the improvement in cognition in men with AD administered testosterone [39; 40].

Whether these changes induced by 17 β -estradiol and testosterone are a direct result of signalling via ER's or AR's is unclear. As indicated above, there is mounting evidence to suggest that the effects of 17 β -estradiol are actually mediated via gonadotropin signalling [12; 19].

Mechanistically, it has been demonstrated that LH regulates A β PP processing towards the amyloidogenic pathway [12] and that A β is in itself a mitogen (see reference [41] and literature cited therein). LH has been shown to mediate mitogenesis since subcutaneous administration of LH induces neurogenesis in the hippocampus of the adult mouse [42], while in sheep there is evidence that GnRH directly, or indirectly via LH, induces neurogenesis in the hippocampus [43]. Elevations in circulating and brain LH (or GnRH) with age-related endocrine dyscrasia could therefore drive the aberrant re-entry of neurons into the cell cycle. Whether this aberrant 'neurogenesis' occurs in resident quiescent totipotent stem cells (e.g. in the dentate gyrus), during the process of neurogenesis (migration and differentiation) or in terminally differentiated neurons has yet to be fully resolved.

Changes in perception of the role of inflammation in Alzheimer's disease

Inflammation as a late step that minimizes disease

Early demonstrations of inflammatory cells in AD brains did not threaten the decades-long primacy of research based on amyloid plaques being the direct primary cause of function

loss in AD, since their association with these plaques [44; 45] was interpreted as facilitating plaque removal [46; 47]. This implied that this inflammatory response was to be encouraged, and immunotherapy designed to promote amyloid removal was investigated, albeit with disappointing results [48; 49]. With plaque removal becoming an increasingly questionable goal [50; 51], and a developing awareness that inflammatory mediators induce, and therefore precede, A β PP [52–57] expression and processing towards the amyloidogenic pathways [58], a fresh approach to understanding the sequence and roles of inflammation and amyloid in AD pathogenesis is warranted.

Inflammation as an early step that initiates disease

An alternative approach, that of inflammation preceding and causing amyloid plaque deposition, begun with the work of Griffin and co-workers [59]. In 1989 this group demonstrated, in AD brains, that overexpression of interleukin 1 (IL-1), a cytokine that functionally overlaps with TNF, had a role in amyloid plaque formation. Four years later Tarkowski [60] reported that TNF levels in CSF from 56 individuals who had mild cognitive impairment, when tracked over a period, predicted which were much more likely to develop into frank AD. Newer studies continue to reaffirm this finding, with markers of inflammation showing in serum and CSF before any indications of increased A β or tau [61; 62]. Another group took advantage of the increased sensitivity of assaying for soluble TNF receptors rather than TNF itself. They found good evidence for levels of these receptors, which TNF induces, in serum and CSF predicting conversion to clinical AD over a 4–6 year period [63]. A more recent example utilized another acute phase protein, clusterin (apolipoprotein J), and found it to be intimately associated with onset, progression, and severity of this disease [64]. Clusterin, which is induced by TNF [65], was present 10 years earlier than fibrillar A β deposition. In addition a new experimental study notably reports that anti-TNF, not TNF, as earlier approaches would have suggested, reduce amyloid plaques in transgenic mice [66]. Taken together, these arguments for inflammation having a key role in the onset, rather than the dissipation, of AD pathology raise the question of what initiates these proinflammatory cytokines increases in the brain in AD.

Endocrine Dyscrasia Mediates the Expression of Pro-inflammatory Cytokines

Reproductive hormones are well known for their cell growth and differentiation properties. Age-related declines in the production of sex steroids and inhibins by the gonads leads to a decrease in negative feedback inhibition on the hypothalamus and pituitary, resulting in an elevation in the production and circulating concentrations of gonadotropins. Changes in the blood-brain barrier and cell cycle described earlier induced by endocrine dyscrasia may be mediated by alterations in expression of TNF (and A β), a molecule with known neurogenic and inflammatory properties.

Gonadotropins

Links between the gonadotropins and TNF in brain function are supported by the findings that TNF, like gonadotropins, is a very pleiotropic cytokine, important in reproductive physiology [67], as well as being a physiological gliotransmitter [68] and central to neurogenesis [69]. Evidence for a role of gonadotropins in regulating TNF expression is demonstrated by the ability of FSH to induce TNF expression in investigations into the illness caused by chronic kidney dialysis [70]. Others, studying the reasons for the exacerbation of rheumatoid arthritis at the onset of menopause, have correlated the high circulating FSH and LH seen at this time with increases in TNF, interleukin-1 β (IL-1 β) and monocyte chemoattractant protein (MCP)-1 [71]. These data are consistent with the anti-gonadotropic actions of leuprolide rendering it an anti-mitotic and anti-inflammatory agent

when it is used to treat endometriosis. In this context leuprolide has been reported to reduce a number of inflammatory cytokines, namely IL-1 β [72], IL-6 [73; 74], and MCP-1 [75], all of which are induced by TNF [76–78]. Moreover, anti-TNF treatment lowers levels of these cytokines [79; 80; 77].

Sex Steroids

Estradiol has been shown to inhibit the release of TNF from monocytes [81] while both estradiol and progesterone reduce TNF expression in mid-brain astrocytes [82]. In addition, estrogen receptor and estradiol agonists inhibit microglial activation, part of the evidence being reduced production of TNF and similar pro-inflammatory cytokines [83]. The signalling pathways have begun to be studied [84; 85]. *In vivo*, outcomes are consistent with these steroids inhibiting TNF production through their capacity to negatively feed back on the hypothalamus and lower gonadotropin-releasing hormone, LH and FSH production. Whether sex steroids directly mediate their effects via nuclear steroid receptors, membrane receptors, or via the regulation of gonadotropins or other hormones is unclear. Functionally, estradiol and progesterone can be regarded as anti-TNF agents that act before TNF is generated. These agents have been reported to protect against AD [35–37], stroke [86; 87], and traumatic brain injury [88–92].

Coupling TNF to Endocrine Dyscrasia and the Pathogenesis of Alzheimer's disease

A considerable basic literature from a number of autonomous groups argues for increased brain TNF [93] having a primary role in the pathogenesis of AD [94–101]. The area has recently been reviewed [102]. It therefore seems plausible from the reasoning in the above paragraphs that these two areas of AD research, hitherto considered unrelated, are in fact the upstream and downstream ends of a single disease mechanism (see Fig. 1). Indeed, both the loss of sex steroids/inhibins and the elevation of GnRH/gonadotropins with age-related endocrine dyscrasia would serve to elevate TNF expression in the brain. This possibility is testable experimentally, and might explain variations in brain TNF levels.

Although, as recently reviewed [102], systemic inflammation and trauma may exacerbate pathogenic brain TNF levels in AD, the explanation for the presence of the underlying TNF in AD brains is little discussed, and still relies on arguments concerning viral infections [103], which does not sit well against the apparent non-infectious nature of AD. Induction of TNF by gonadotropins could explain why changes achieved in A β deposition and cognition with leuprolide treatment [12; 13], are consistent with those reported for anti-TNF approaches in similar circumstances [97; 104; 101; 66]. At this stage it is not possible to determine whether endocrine dyscrasia is regulating cell cycle signalling independent of TNF. It should be noted, however, that some 15 genes integral to TNF signalling have been found to regulate the G₂/M stage of the human cell cycle [105]. Interestingly, a single nucleotide polymorphism in TNF has been associated with the risk of developing AD; that risk was further increased in those individuals positive for APOE E₄ [106], a gene involved in cholesterol metabolism and steroidogenesis.

Oxytocin, TNF, anxiety disorder and aggression

Anxiety and aggression are often observed with AD, and after stroke and traumatic brain injury. The literature clearly associates these changes with increased TNF in a range of circumstances. For example, testosterone cells isolated from individuals with a generalized anxiety state generate more TNF on *in vitro* activation [107], and the ability of endotoxin-triggered human monocytes to generate TNF *in vitro* associates with aggressiveness [108]. Most strikingly, double TNF receptor knock-out mice essentially lack both anxiety and aggression [109]. These and similar data are consistent with the high anxiolytic capacity of

anti-TNF biological agents in patients with rheumatoid arthritis [110] as well as in a mouse model of chronic gastrointestinal inflammation [111]. Inflammatory bowel disease is a well-known cause of anxiety disorder in humans [112]. The well-known anxiolytic actions of progesterone [113] may be mediated via TNF, with the decline in circulating progesterone with endocrine dyscrasia resulting in elevations in TNF. Progesterone has not been tested as a treatment for AD.

In contrast to TNF, oxytocin attenuates experimental anxiety states [114–116], and its levels in human CSF have been inversely associated with life history of aggressive behavior [117]. This is plausibly explained by the ability of oxytocin to reduced production of TNF by monocytes from human volunteers [118]. Evidence for oxytocin being the driving force behind the effects of social interaction (i.e.v. oxytocin receptor inhibitor cancelled the effect), and its insufficiency explaining the effects of social isolation (i.e.v. oxytocin injection cancelled the effect) [119] is compelling. It may also explain, through the capacity of oxytocin to inhibit TNF production [118], why long-term social isolation exacerbates the impairment of spatial working memory in A β PP/PS1 transgenic mice [120]. In addition, social isolation makes experimental stroke worse, decreasing post-stroke survival rate and exacerbating infarct size and edema development [121]. The authors explained their data in terms of IL-6, a cytokine induced by TNF, being higher in the socially isolated animals. So far as we are aware oxytocin has not yet been tested to treat AD, stroke or traumatic brain injury.

Implications for understanding these diseases, and devising therapies

These widespread functional links between the gonadotropins, sex steroids and TNF imply that it is worth investigating all three together when developing an understanding of, and therapy for, neurodegenerative diseases. Anti-TNF agents have been tested in an experimental AD model [66] and open-labeled human trials [122; 123], in an experimental traumatic brain injury model [124], and small, but impressive, open-labeled human stroke trial [125]. In a significant case report of TNF suppression, a patient being treated with the anti-TNF agent etanercept for ankylosing spondylosis prior to T7 complete paraplegia demonstrated remarkable sensory-motor recovery, improving from A to D on the American Spinal Injury Impairment Scale (AIS) within the first year [126].

A point of immediate interest arises from a report that TNF generation in the brain, once initiated, continues there for much longer (months) than it does systemically (hours) [127], exposing a specific target for anti-TNF agents for a much longer period in brain than in the rest of the body. This could rationalize the long reported intervals between stroke onset and apparently successful treatment with an anti-TNF agent [125]. For these reasons synergistic and other therapeutic studies using leuprolide, estrogens, progesterone and oxytocin in conjunction with anti-TNF agents are warranted.

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Basic Alzheimer's disease pathway

Rational therapies

Figure 1.

Model of the convergence of dyotic signalling (elevated gonadotropins, suppressed sex steroids) on TNF and cell cycle dynamics as functionally important downstream links mediating neurodegeneration and dysfunction. Based on this model, rational[32] therapies are proposed for the treatment of AD.