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HEALTHY AGING RESEARCH

Supporting evidence for using Perispinal Etanercept to inhibit TNFα when treating neuropathologies including dementia, chronic stroke, neuropathic pain or traumatic brain injury: Role of TNF in neuropathologies and in particular in Alzheimer's disease (Part II)

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Abstract

Part II of this three-part review examines the evidence for the involvement of the pro-inflammatory cytokine, Tumour Necrosis Factor-alpha (TNFα) in neuropathologies with a particular focus on Alzheimer's Dementia (AD). It helps to underpin the support for Part III – establishing the basis for using anti-TNF therapy and why it is justified to target and treat these health problems, including chronic stroke, dementias, neuropathic pain or traumatic brain injury. All of these can become chronic illnesses and are of major incidence with a grossly unmet need to improve their treatment.

Part I established the role of TNFα as a direct regulator of neuronal synaptic activity. It is in this context that Part II analyses abnormalities in TNF levels associated with disease, using AD as an example of the consequence that can arise from TNF-induced changes in the brain. Parts I and II then provide support for clinical application of anti-TNF therapy, which is discussed in Part III not only for treating the dementias, but also its great benefits in reducing long-term pain during rehabilitation from traumatic brain injury or chronic stroke, areas where Perispinal Etanercept therapy holds special significance.

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Late Onset Alzheimer's Dementia as an example of global depression in brain function, showing many aspects of long-term depression

To reiterate from Part I, the evidence is consistent with a role for TNF in inducing a rapid rise in CP-AMPARs in a dose-responsive manner, which contributes to excitotoxic vulnerability, and hence to the ensuing loss of brain function. TNFα also regulates neuronal inhibition by affecting the endocytosis of the GABA-A receptor, the principle mediator of "fast" inhibition in the brain. It is in this context that the TNFα-induced changes in neuronal circuit responses occur very rapidly, within 15–60 minutes and can be completely inhibited by the presence of soluble TNFR1 receptor [1–5]. These observations are consistent with the effects of the anti-TNFα targeted Perispinal Etanercept (PSE) therapy, which are also rapid, with responses detected in treated patients occurring over a similar fast time course [6–12].

It is becoming possible to determine early and with high level accuracy those amongst us who will go on

to develop Alzheimer's disease [13–15]. Diagnostic biomarkers are becoming defined that will predetermine up to 20 years before onset those who are at risk of developing dementia later in life. Thus, early diagnosis can now be carried out several decades before the first realisation of disease onset, previously only able to be diagnosed by observing those classical behavioural and mental symptoms typically associated with dementia. With these advances has also come the ready availability of screening for dementia at the very early stage in the population by using simple blood tests [14, 15]. However, as a consequence of the breakthrough in diagnosis of dementia, there arises a currently unmet need for early intervention treatment that will prevent the disease from progressing.

Tentative evidence for this was presented in that an analysis of 42,193 patients with rheumatoid arthritis for those who developed Alzheimer's disease showed significantly reduced incidence (adjusted odds ratio (OR) 0.440; 95% confidence interval (CI) 0.223–0.868; p=0. 0178) [16]. The risk of AD was not affected by exposure to sulfasalazine, prednisone or rituximab and of the anti-TNF therapies used, Etanercept (Enbrel) treatment was found superior with nearly 70% reduced incidence of dementia compared to the background control population [16]. Such a treatment, if proven to be effective in trials would have enormous impacts, alleviating the burden of socioeconomic stress caused by dementia. Furthermore, other neurological pathologies including chronic stroke, traumatic brain injury and neuropathic pain will benefit greatly from this therapy as is shown by the evidence outlined below.

Neurodegenerative disease and post-injury environments are characterised by abnormally high levels of TNF that have been found responsible for the neuronal cytotoxicity and dysfunction [17–21] and TNF can directly induce neuronal cell death [22–25].

The role of TNF in Alzheimer's disease: β amyloid protein (Aβ) and its relationship to TNFα production

A link between beta (β)-amyloid (Aβ) protein deposition and the plaque formation typically associated with Alzheimer's disease has been a long standing dogma with amyloid plaque as the causative factor in dementia. This has culminated in the abject failure by the major pharmaceutical companies recently using antibodies targeting the beta-amyloid protein ($A\beta_{1\text{-}42}$) to prevent or ameliorate Alzheimer's disease (Pfizer and Johnson & Johnson: Bapineuzumab; Eli Lilly: Solanezumab). Consequently, it is becoming clear that amyloid deposition is not causally associated with AD but rather a by-product of the disease, which may in fact, be nature's way of minimising the damage to the neurons caused by the soluble form of the Aβ protein by removing it as inactive insoluble aggregates [26, 27].

Synaptic plasticity mechanisms, including those underlying the process of LTP or LTD of glutamatergic transmission, constitute the neuronal basis for learning and memory [28] and they are highly vulnerable to rapid disruption by soluble Aβ species derived either by chemical synthesis ([29–32]; Figure 1) or from cells that naturally secrete them after the cleavage of the amyloid precursor protein (APP) by the β- and γ-secretase enzymes [33]. Recent research supports a key role for the soluble oligomeric forms of the amyloid protein, particularly A_{β} dimers, in amyloid effects on synaptic plasticity [34].

What has only become more apparent recently is a connection between the excess production of the soluble amyloid protein, $A\beta_{1\text{-}42}$ and the increased production of TNFα as part of a vicious cycle of brain damage [35]. Several studies have shown that beta-amyloid ($A\beta_{1\text{-}42}$) inhibits LTP (i.e., memory). In many studies now reported, $A\beta_{1\text{-}42}$ has been found to inhibit the induction of hippocampal LTP [29, 30, 36–43]. It is also known that $A\beta_{1\text{-}42}$ provokes a microglial-mediated inflammatory response that contributes to the neurodegeneration characteristic of Alzheimer's disease [44]. However, TNFα has a key role in $A\beta_{1\text{-}42}$ inhibition of LTP. Thus, the suppression of LTP by $A\beta_{1\text{-}42}$ was absent in mutant mice null for TNF receptor type 1 (TNF-R1), and it was also prevented by the inhibitors of TNFα ([45]; reviewed in [34]). In addition, exogenous TNFα inhibited LTP induction and the inhibition of LTP by TNFα involved activation of mGluR1 and p38 MAP kinase, the same receptor required for the $A\beta_{1\text{-}42}$-mediated inhibition of LTP induction [45].

The GluN2B NMDAR is also involved in the stress-mediated inhibition of memory function [46]. Evidence that TNFα, once again, is involved in the deleterious action, also involving Aβ, was provided when it was shown that TNF antagonists are able to prevent the Aβ inhibition of plasticity and the abrogation of a similar disruptive effect of TNF by using a GluN2B-selective antagonist [47]. Moreover, at nearby synapses that were resistant to the inhibitory effect of TNF, $A\beta_{1\text{-}42}$ did not significantly affect plasticity. Thus, the evidence is clearly mounting that cognitive impairment in Alzheimer's is due to synaptic dysfunction caused by the accumulation of soluble Aβ-peptide long before widespread synaptic loss and neurodegeneration occurs. This process involves soluble Aβ oligomers, which can rapidly disrupt synaptic memory mechanisms at extremely low concentrations and act by inducing TNF production [45].

In this context, one of the most exciting findings derives from a very recent study that compared infusing either the fibrillar (FAβ) or the soluble form of $A\beta_{1\text{-}42}$ for its effects on the rat brain over extended periods [48]. These studies showed that the soluble form ($A\beta_{1\text{-}42}$) was much more potent in its effects on the expression of the pro-inflammatory factors, toll-like receptor 4 (TLR-4) and TNFα, with activation of NF-κB signalling. Taken together, the results from these studies clearly indicate that the soluble Aβ protein oligomers are the neurotoxic form and this neurotoxicity proceeds via TNF activation of the NF-κB-mediated pro-inflammatory response [48]. More recently, TNFα was shown as the mediator of Aβ oligomers in mice and monkeys to induce synapse loss and memory impairment [49], whereby TNFα/TNFR1 signalled inside brain cells by activating the double stranded RNA dependent protein kinase, PKR. It also led to increased phosphorylation of the Insulin Receptor Substrate, IRS-1, important for insulin signalling, such that IRS-1 became serine phosphorylated, inhibiting IRS-1 recruitment of the PI3K/Akt signalling, similar to that which occurs in insulin resistant cells in diabetes [49].

TNF increases Aβ secretase levels to promote production of soluble amyloid protein. The vicious cycle of brain damage

Generation of $A\beta_{1\text{-}42}$, the harmful, toxic, activated form of beta-amyloid protein, occurs through the proteolysis of the Amyloid Precursor Protein (APP), a nerve cell surface membrane protein, by the sequential actions of the β- and γ-secretase enzymes. The cytokines, IFN-γ, IL-1β, and TNF specifically increase the expression of APP on astrocytes [50–52] and stimulate γ-secretase activity, concomitant with increased production of $A\beta_{1\text{-}42}$ [53]. Subsequently, IFN-γ and TNF were shown to enhance $A\beta_{1\text{-}42}$ production from APP-expressing astrocytes and cortical neurons, and the numbers of astrocytes expressing IFN-γ was increased and IFN-γ induced TNF production [54]. In addition, TNF signalling stimulated the β-site APP-cleaving enzyme (BACE-1, or β-secretase) expression, thereby enhancing β-site processing of APP in astrocytes. Furthermore, TNFR1 depletion reduced BACE-1 activity [55]. Logically, therefore, anti-TNF agents should, among their other actions, be effective APP cleavage inhibitors. Results obtained in mice with long-term inhibition of TNF are functionally consistent with this [56], and it was concluded that one physiological role for TNF in the brain is to maintain APP and Aβ homeostasis, with excessive TNF generation, from whatever origin, upsetting this to the detriment of synaptic function because Aβ is then produced too rapidly.

Once generated excessively, $A\beta_{1\text{-}42}$ induces more TNF, which drives the pathology associated with Alzheimer's disease. Thus, to summarise the evidence above, TNF has three directly interlocking pathogenic roles in encephalopathies in which TNF levels in the brain are elevated: (i) TNF increases the APP levels to cause pathology; (ii) TNF participates in driving APP into $A\beta_{1\text{-}42}$, by increasing secretase expression; and (iii) TNF, by inducing $A\beta_{1\text{-}42}$, which in turn, mediates many of its harmful effects, predominantly acting in a feed-forward manner to further increase the levels of TNF production from the glial cells.

Clearly, all of these actions of TNF make it a very attractive therapeutic target. Logically, the $A\beta_{1\text{-}42}$-induced TNF can be expected to add to the TNF pool inducing APP, as well as increasing its breakdown to

$A\beta_{1-42}$. These links, once initiated, between the production of TNF and $A\beta_{1-42}$ and the positive feedback loop will combine in concert with any additional TNF production derived from over-expression of inflammatory responses to exacerbate the continued decline and inevitable worsening in brain function detected during Alzheimer's disease (Fig. 1). In this regard, Alzheimer's typifies the neuropathological role of TNF and as one of the imminent health crises facing the human race, as we all get older, demands that we pay increased attention to it and focus on clinical development of interventions such as those outlined in Part III.

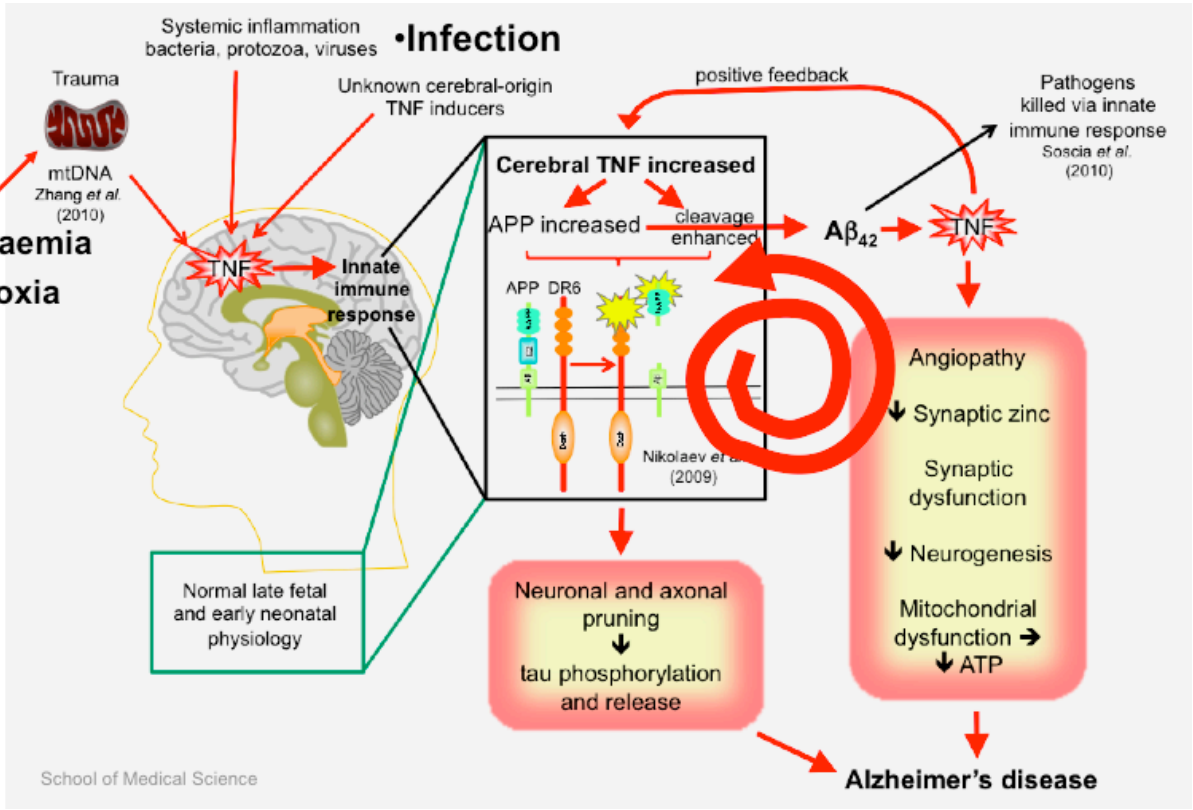

Figure 1. Causative stress factors for long-term depression in the brain such as traumatic brain injury, ischaemia/hypoxia, infection or other lead to damage and increased production of TNF, which in turn increases expression of the Amyloid Precursor Protein (APP), whose proteolytic cleavage produces the beta-amyloid peptide, $A\beta_{1-42}$ (or $A\beta_{42}$) that feeds back to further exacerbate increased levels of TNF production. This cycle (indicated by the circling red arrow), if left unchecked, will result not only in LTD, but also neuropathology due to cell death and loss of neurons causing dementia. Modified from [57].

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