Journal of Alzheimer's Disease 24 (2011) 1–5
DOI 10.3233/JAD-2011-110266
IOS Press

Short Communication

TNF and Leptin Tell Essentially the Same Story in Alzheimer's Disease

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Accepted 6 April 2011

Abstract. Both tumor necrosis factor (TNF) and leptin are, independently, under investigation as the central mechanism for Alzheimer's disease. The wider literature provides every indication that both mediators are part of the same pathways thought to cause functional loss in this condition. This association, which has not been specifically addressed in the Alzheimer's disease literature, may be a useful link to expedite future study into the pathogenesis of this condition.

Keywords: Alzheimer's disease, inflammation, leptin, tumor necrosis factor

It is essential to understand the pathophysiology of Alzheimer's disease (AD), since it is a requirement for the development of a successful treatment. With the long-standing amyloid-β (Aβ) paradigm being increasingly questioned [1–3], the interest continues to shift to soluble mediators, rather than histological changes, as the primary mechanism of this condition. As reviewed [4], in recent years one approach has focused on a primary harmful role for tumor necrosis factor (TNF), and treatment based on neutralizing it with specific biological agents already in clinical use for other conditions, such as rheumatoid arthritis [5].

TNF is made by an exceptionally wide range of cell types, including, in the brain, microglia, astrocytes and neurons, as well as adipocytes, whereas leptin originates from none of these except adipocytes. Both TNF [6] and leptin [7] exhibit circadian rhythmicity in the rat brain. Unlike other inflammatory mediators, leptin is readily detectable in the circulation under normal conditions, and fluctuates to reflect the energy status of the individual. Leptin has historically been associated with obesity, which has been argued to be an inflammatory condition [8].

Since the demonstration that leptin lowers Aβ loads [9], and its reconstitution by subcutaneous administration causes a striking cognitive improvement in an individual with a harmful leptin gene mutation [10], considerable interest has arisen about its role in AD [11–13]. This raises the question of whether investigating leptin in an AD context is uncovering a novel mechanistic pathway and putative treatment, as seems to have been accepted, or whether it covers essentially the same ground as the research that argues for a central role of TNF in the pathogenesis of this disease. The latter possibility is plausible, since both cytokines are known to converge in the literature of chronic inflammatory states. Given that AD is being increasingly being seen in this light, it warrants exploring the known interactions of TNF and leptin in examples of chronic inflammatory states in general, and their *in vitro* correlates.

Exposing patients to high TNF levels acutely increases serum levels of leptin [14], but this change is transient, since it arises from depletion of existing stores within adipocytes [15]. In contrast, incubating

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ISSN 1387-2877/11/$27.50

adipocytes with TNF or interleukin-1β for 24–48 h reduces both message and protein release of leptin [16, 17]. This is borne out *in vivo*, with lowered serum leptin levels in patients with tuberculosis, a chronic inflammatory state known to be associated with increased TNF levels [18]. Likewise, serum levels of leptin have been reported to be inversely correlated with C reactive protein (CRP)—an acute phase protein induced by TNF [19] and widely used as a marker for systemic inflammation in patients with rheumatoid arthritis [20]. Since CRP is raised in the cerebrospinal fluid (CSF) and serum of AD patients very early in the course of their disease [21, 22], this inverse relationship between leptin and CRP is consistent with serum leptin levels being high when there is a low risk of developing AD [23], and low in severe dementia [11]. It is also consistent with higher TNF levels in CSF being able to predict, when tracked over a period, mild cognitive impairment developing into AD [24].

Leptin has been proposed to be a plausible treatment for AD because experimentally it can improve a range of changes seen in this condition. Examining this treatment possibility and understanding the outcome more deeply than at present requires taking into account its relationship to TNF. For example, administering leptin reduces the *in vivo* capacity to generate TNF (by 47% in primates) [25], and patients routinely treated with a commercial anti-TNF biological agent, infliximab, show increased serum leptin levels [26]. This outcome is consistent with experiments in which mice rendered leptin deficient by 48 h fasting were more sensitive to endotoxin (they generated more TNF), an effect annulled by leptin supplementation [27]. Unrelated *in vitro* studies have demonstrated endotoxin-induced TNF to be released into culture medium by prior exposure of microglia to leptin, but this was associated with depletion of cellular stores of TNF, not new protein production [28], and therefore unlikely to be relevant to the pathogenesis of a chronic inflammatory state. This is reminiscent of the acute reverse effect, discussed above, of TNF on leptin levels [15].

Many of the detrimental changes leptin can improve have been shown to be caused by excessive TNF and, where tested, to be ameliorated by anti-TNF treatments or TNF receptor (TNFR) depletion. For example Aβ and tau are reduced by both leptin [9] and infliximab, a specific anti-TNF biological in large-scale clinical use [29]. Likewise, both leptin [30] and etanercept [31], another anti-TNF agent widely used in the clinic, are anxiolytic in mouse models, and both leptin [9] and TNFR1 depletion [32] decrease the activity of β-secretase, a key enzyme in amyloid-β protein precursor cleavage. Moreover, TNFR1 depletion also prevents memory and learning deficits in a mouse AD model [32], as does leptin [33].

Inflammation can repress neurogenesis [34, 35], a phenomenon now appreciated to be interrupted in AD, and able to be influenced by both TNF [36] and leptin [37]. Excess TNF suppresses proliferation (via TNFR1) [38], a finding that, from the pattern emerging here, would have successfully predicted the observation that chronic administration of leptin, acting like anti-TNF, increases it [37]. The morphology of dendritic spines of hippocampal neurons is differentially influenced by TNF [39] and leptin [40]. Without providing detail, it suffices to say here that research on both TNF and leptin have generated literatures to do with mediating and controlling minutiae of neuronal function such as NMDA channels, AMPA receptors, long-term potentiation, and synaptic plasticity. An *in vivo* reflection of the pattern is the ability of both anti-TNF antibody [41] and leptin [42] to inhibit seizures induced by administration of pentylenetetrazole (PTZ), a GABAergic antagonist). PubMed reveals 36 papers on TNF and synaptic plasticity and 32 on leptin and synaptic plasticity, yet remarkably no synaptic plasticity paper referring to both. References [43] (TNF) and [44] (leptin) are examples of an opportunity to compare them, in this case concerning their involvement in AMPA receptor trafficking, being missed.

Finally, we note that the unrecognized functional parallels between TNF and leptin concern their molecular signaling pathways. Activation of glycogen synthase kinase-3 (GSK-3) the beta form of which, GSK-3β, is particularly abundant in the hippocampus, has recently been reasoned to be a key priming event for the deficits in memory formation in the early stages of AD, as well as neurodegeneration in its later stages [45]. Laboratory models have demonstrated that TNF activates GSK-3β [46, 47], whereas leptin prevents its activation [48, 49]. We can also expect specific anti-TNF agents to have also prevented this activation had they been tested. Likewise, the reduction of Aβ production and tau phosphorylation by leptin depends on AMPA-activated protein kinase (AMPAK) [50], an enzyme that TNF suppresses [51]. These contrasting observations rationalize anti-TNF [29] sharing with leptin [50], its capacity to reduce with Aβ and phosphorylated tau.

These examples indicate a global opposing symmetry of function relevant to AD, not previously noted, between TNF and leptin. It seems clear, therefore, that the same pathway is under examination in both of these currently separate subsets of the

Table 1

Parameter	Effect of leptin	Effect of TNF
associated with low risk of AD	high leptin [23]	low TNF [24]
leptin levels	increased	reduced by TNF [16, 17]
TNF levels	reduced by leptin	increased
correlation with CRP	inverse [20]	direct [19]
memory and learning	improved by leptin [33]	reduced by TNF (TNF evidence [52]) (TNFR1 KO evidence [32]) (anti-TNF evidence [52])
anxiety	reduced by leptin [30]	increased by TNF (anti-TNF evidence [31])
Aβ and phosphorylated tau	lowered by leptin [9]	increased by TNF (anti-TNF evidence [29])
β-secretase activity	reduced by leptin [9]	increased by TNF (anti-TNF evidence [32])
neurogenesis	increased by leptin [37]	reduced by TNF [36]
dendritic spine growth	increased by leptin [40]	decreased by TNF (TNFR1 iRNA evidence [39])
GSK-3 activation	reduced by leptin [48, 49]	increased by TNF [46, 47]
AMPK activation	leptin's AD effects depend on it [50]	suppressed by TNF [51]
PTZ-induced seizures	prevented by leptin [42]	driven by TNF (anti-TNF evidence [41])
treatment proposals	Leptin reasoned as a rational treatment for AD [11, 33, 53]	Anti-TNF reasoned as a rational treatment for AD [29, 54, 55]

AD literature, and neither can be fully understood in isolation. Clinical interest will focus on whether a daily subcutaneous injection of leptin [10], a hormone with many metabolic functions, will achieve as much improvement, and in the lean as well as the obese, leptin-resistant, patient, as will the less frequent injection of agents that specifically inhibit TNF, particularly when administered so as to target the brain. Therapeutic synergy between anti-TNF and leptin in AD and similar diseases is probably the main area of clinical investigation made possible by being aware of the wider literature.

In summary, the wider literature, as summarized in Table 1, predicts that the TNF and leptin studies on understanding and treating AD are integral parts of the same approach. The presence of these parallel but independent AD literatures, seemingly unaware of their common focus, reinforces the likelihood of the pathways in which they are both involved being central to the pathogenesis, and therefore treatment, of this condition.

ACKNOWLEDGMENTS

The authors received no financial or material support for this research.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?*id* = 843).

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