

ASSOCIATE EDITOR: DAVID R. SIBLEY

Tumor Necrosis Factor-Induced Cerebral Insulin Resistance in Alzheimer's Disease Links Numerous Treatment Rationales

Ian Clark, Craig Atwood, Richard Bowen, Gilberto Paz-Filho, and Bryce Vissel

Research School of Biology, Australian National University, Canberra, Australia (I.C.); Department of Medicine, University of Wisconsin-Madison School of Medicine and Public Health, Madison, Wisconsin (C.A.); School of Exercise, Biomedical and Health Sciences, Edith Cowan University, Joondalup, Australia (C.A.); OTB Research, Charleston, South Carolina (R.B.); John Curtin School of Medical Research, Australian National University, Canberra, Australia (G.P.-F.); and the Neurodegeneration Research Group, Garvan Institute of Medical Research, Sydney, Australia (B.V.)

Abstract	1005
I. Introduction	1005
II. Gonadotropins, sex steroids, tumor necrosis factor, and Alzheimer's disease	1005
III. Tumor necrosis factor and Alzheimer's disease	1006
IV. Tumor necrosis factor, amyloid β , and τ	1007
V. Insulin	1008
A. Insulin in basic biology and the brain	1008
B. Insulin resistance and Alzheimer's disease	1008
C. Tumor necrosis factor and insulin resistance	1009
D. Functional links of glucagon-like peptide-1 to insulin resistance	1010
VI. Tumor necrosis factor and glycogen synthase kinase-3	1010
VII. Tumor necrosis factor and mitochondrial dysfunction	1011
VIII. Tumor necrosis factor and progenitor cells	1011
A. Progenitor cells, tumor necrosis factor, and insulin resistance	1011
B. Clock genes, controlled by tumor necrosis factor, govern progenitor activity	1012
IX. Streptozotocin	1013
A. Streptozotocin model for diabetes and Alzheimer's disease	1013
B. Streptozotocin induces tumor necrosis factor	1013
X. The broader picture—stroke, traumatic brain injury, and infectious disease	1014
XI. Therapeutic implications	1014
A. Specific inhibition of tumor necrosis factor	1014
B. Nonspecific inhibition of tumor necrosis factor	1015
1. Thalidomide and curcumin	1015
2. Minocycline	1015
3. Erythropoietin	1015
C. Administering leptin as a counter to insulin resistance	1016
D. Administering insulin as a counter to insulin resistance	1017
E. Glucagon-like peptide-1 mimetics and dipeptidyl peptidase-4 inhibitors as counters to insulin resistance	1017
F. Glycogen synthase kinase-3 antagonists	1017
H. Apolipoprotein E mimetics and bexarotene	1018
XII. Conclusions	1019
References	1019

Address correspondence to: Prof. Ian Clark, Division of Medical Science and Biochemistry, Research School of Biology, Australian National University, Canberra ACT 0200, Australia. E-mail: ian.clark@anu.edu.au
This article is available online at <http://pharmrev.aspetjournals.org>.
<http://dx.doi.org/10.1124/pr.112.005850>.

Abstract—The evident limitations of the amyloid theory of the pathogenesis of Alzheimer's disease are increasingly putting alternatives in the spotlight. We argue here that a number of independently developing approaches to therapy—including specific and non-specific anti-tumor necrosis factor (TNF) agents, apolipoprotein E mimetics, leptin, intranasal insulin, the glucagon-like peptide-1 mimetics and glycogen synthase kinase-3 (GSK-3) antagonists—are all part of an interlocking chain of events. All these approaches inform us that inflammation and thence cerebral insulin resistance constitute the pathway on which to focus for a successful clinical outcome in treating this disease. The key link in this chain presently absent is a recognition by Alzheimer's research community of the long-neglected history of TNF induction of insulin resistance. When this is incorporated into the bigger

picture, it becomes evident that the interventions we discuss are not competing alternatives but equally valid approaches to correcting different parts of the same pathway to Alzheimer's disease. These treatments can be expected to be at least additive, and conceivably synergistic, in effect. Thus the inflammation, insulin resistance, GSK-3, and mitochondrial dysfunction hypotheses are not opposing ideas but stages of the same fundamental, overarching, pathway of Alzheimer's disease pathogenesis. The insight this provides into progenitor cells, including those involved in adult neurogenesis, is a key part of this approach. This pathway also has therapeutic implications for other circumstances in which brain TNF is pathologically increased, such as stroke, traumatic brain injury, and the infectious disease encephalopathies.

I. Introduction

Despite its increasingly high incidence, harmful effects on people and society, and the considerable funding directed toward understanding its mechanism, differing ideas on the driving force of Alzheimer's disease (AD¹) remain unresolved. For decades, the bulk of the research effort has been focused by the wealth of logic in the idea that amyloid β (A β), the major neurohistological hallmark of this condition, triggers the onset of disease. This approach was very encouraging in mouse studies (Huang et al., 1999; Hung et al., 2008), but the negative outcome of recent human trials, including when amyloid was confirmed to have been reduced (Holmes et al., 2008; Green et al., 2009; Salloway et al., 2009; Extance, 2010), has led to much reassessment and repositioning that has led to lucid arguments for nonfailure of the amyloid model itself (Karran et al., 2011; Sperling et al., 2011). These negative human trials may have also led to wider acceptance of AD research that has thrown the net wider, taking into account the pathophysiology this disease shares with a range of conditions, both infectious and noninfectious. This has allowed ideas such as the cerebral insulin resistance model (de la Monte and Wands, 2008) to gain warranted prominence (Correia et al., 2011; McNay and Recknagel, 2011).

As discussed below, two therapeutic approaches already realized to be consistent with the model we are proposing are intranasal insulin and parenteral glucagon-like peptide-1 (GLP-1) mimetics. A major purpose of this review is to summarize the large volume of pub-

lished evidence that, taking into account TNF and functionally similar cytokines, dramatically reinforces the likelihood that cerebral insulin resistance is indeed central, albeit somewhat downstream, in the etiology of this disease. The AD literature on leptin is also consistent with this. Here we present the case that a number of proposed treatments for AD are functionally linked, either by their capacity to lower insulin resistance or to deal with the consequences of this event (Fig. 1). These treatments include leuprolide acetate, various ways to reduce TNF levels (specific anti-TNF biological agents, and nonspecific down-regulators of TNF production (thalidomide, curcumin, and their derivatives; minocycline; erythropoietin variants; and sex steroids), the GLP-1 mimetics and dipeptidyl peptidase-4 (DPP-4) inhibitors, leptin, insulin itself, as well as glycogen synthase kinase-3 β (GSK-3 β) inhibitors. All are under active investigation by researchers presently coming from different perspectives.

As we also discuss, not only are extensive links between TNF and AD now reported, but also between TNF and gonadotropins as well as TNF and cell division, insulin resistance, type 2 diabetes (T2DM), mitochondrial dysfunction, and the pathologic condition caused by intracerebroventricular streptozotocin. These well documented aspects of the repertoire of TNF activity, which we suggest should become common currency in AD research, are expanded upon in this review.

II. Gonadotropins, Sex Steroids, Tumor Necrosis Factor, and Alzheimer's Disease

Considerable evidence exists that elevated levels of the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are associated with neurodegenerative disease. For examples, total brain levels of A β , a traditional histological marker for AD, are increased by high LH levels [such as after ovariectomy (Frye et al., 2007)], and decreased by the gonadotropin superagonist leuprolide acetate (Bowen and Atwood, 2004; Casadesus et al., 2006; Berry et al., 2008). Cogni-

¹Abbreviations: A β , amyloid β ; A β PP, amyloid β precursor protein; ACT, α 1-antichymotrypsin; AD, Alzheimer's disease; Akt, protein kinase B; apoE, apolipoprotein E; BBB, blood-brain barrier; CD14, cluster determinant 14; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; DPP-4, dipeptidyl peptidase-4; EPO, erythropoietin; FSH, follicle-stimulating hormone; GLP-1, glucagon-like peptide-1; GSK, glycogen synthase kinase; IFN, interferon; IL, interleukin; LH, luteinizing hormone; NP12, 4-benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione; SB216763, 3-(2,4-dichlorophenyl)-4-(1-methyl-1H-indol-3-yl)-1H-pyrrole-2,5-dione; SZT, streptozotocin; T2DM, type 2 diabetes; TBI, traumatic brain injury; TNF, tumor necrosis factor.

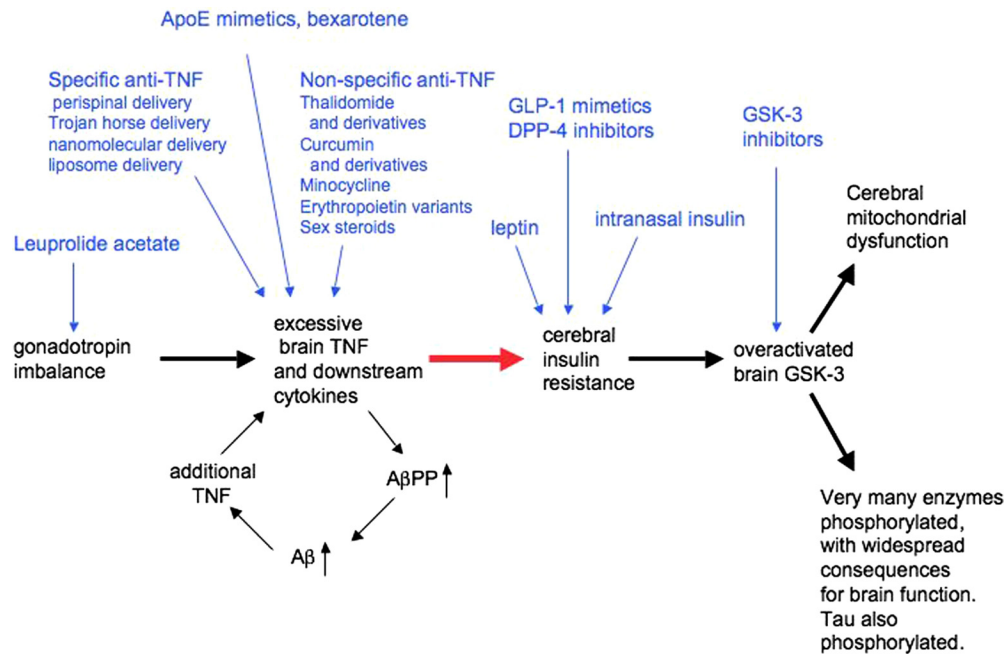


FIG. 1. The overarching inflammatory pathway to Alzheimer's disease that becomes evident once it is appreciated that TNF induces insulin resistance (red arrow). Treatment concepts now in development (in blue) all address this pathway.

tive function follows the same pattern, with low LH levels improving memory and cognition and high levels making them worse, provided LH receptors are present (Casadesus et al., 2006, 2007; Bryan et al., 2010; Ziegler and Thornton, 2010; McConnell et al., 2012). We have discussed previously the developing field of physiological sex hormone replacement therapy for AD treatment (Clark and Atwood, 2011). This is rationalized, at least in part, by the capacity of both estradiol and progesterone to reduce TNF expression in astrocytes (Kipp et al., 2007). These hormones have been reported to protect against AD (Honjo et al., 1989; Asthana et al., 2001).

Gonadotropins can regulate production of TNF, which was shown to alter cell cycle dynamics by the group that first described it (Darzynkiewicz et al., 1984). In brief, FSH has been reported to induce TNF in vitro (Iqbal et al., 2006), and high LH and FSH levels have allowed the rationalization, through their association with high TNF and IL-1 β , of the onset or exacerbation of rheumatoid arthritis in women at menopause (Kåss et al., 2010). As we have noted (Clark and Atwood, 2011), the antigonadotropic actions of leuprolide render it an anti-mitotic and anti-inflammatory agent when used to treat endometriosis. In this context, leuprolide has been reported to reduce a number of inflammatory cytokines [e.g., IL-1 β (Meresman et al., 2003), IL-6 (Ferreira et al., 2010; Ficicioglu et al., 2010), and monocyte chemoattractant protein-1 (Khan et al., 2010)], all of which are induced by TNF (Shalaby et al., 1989; Charles et al., 1999; Mueller et al., 2010) and reduced by anti-TNF treatment (Brennan et al., 1989; Redl et al., 1996; Charles et al., 1999). Insulin resistance, commonly a TNF-induced state, and now regarded to be central to AD (see section V.B), is

routinely seen in late pregnancy (Ryan et al., 1985). Late pregnancy is also a time of physiological low-grade inflammation (de Castro et al., 2011) that is plausibly regulated by the interactions of gonadotropins and TNF.

Not enough is yet known about the integration of these reproductive hormones into broader physiology and disease. Nevertheless, they already give an encouraging lead into how TNF might become excessive very early in AD (Clark and Atwood, 2011). As was TNF for years, in most minds these widely published hormones are still in a nomenclature straightjacket arising from their first description. This generates popular assumptions and limits enquiry into their relevance across wider biology. The potential for their involvement is there, because LH receptors, for example, are present on an astonishing array of cell types, ranging from thymocytes and peripheral lymphocytes (Rao et al., 2003) and macrophages (Sonoda et al., 2005) through endothelial cells (Tsampalas et al., 2010) to neurons and various microglial cells (Rao et al., 2003), as well as where one would expect them to be from the gonadotropin function of LH.

III. Tumor Necrosis Factor and Alzheimer's Disease

The literature often gives the impression that TNF is the only inflammatory cytokine, and most of this review, for the sake of brevity, is no exception. TNF is at present widely regarded, mainly from experience in the field of rheumatology (Brennan et al., 1989; Charles et al., 1999), as the master cytokine that starts the inflammatory cascade. Nevertheless, mediators such as the inter-

leukin-1s (of which IL-1 β is the form released into extracellular fluids) are also inflammatory and may well develop their own literature parallel to that described here for TNF. IL-1 is the most advanced in this regard (Griffin et al., 1989; Kitazawa et al., 2011). A mutual dependence of these two cytokines is evident in the brain, with reports of anti-TNF agents limiting the release of IL-1 (Terrando et al., 2010) and TNF levels being reduced when IL-1 signaling is blocked (Kitazawa et al., 2011). A number of higher numbered interleukins, such as IL-12, IL-17, and IL-22, have become functionally linked with TNF but are, so far, little studied in the brain. It also warrants noting, for clarity, that the term TNF (Carswell et al., 1975) is identical to TNF- α , the commonly seen suffix being a now-meaningless relic from when lymphotoxin was, for a limited period some years ago, referred to as TNF- β .

Although some still regard inflammation in AD as solely a secondary downstream consequence of A β generation (as reviewed by Zotova et al., 2010), evidence continues to accumulate (for review, see Clark et al., 2010) for excess cerebral TNF, and therefore the cascade of cytokines it initiates, to be viewed as an essential preillness step in its pathogenesis. Some time ago, higher cerebrospinal fluid (CSF) levels of TNF from 56 subjects with mild cognitive impairment, but not 25 age-matched controls subjects, were reported to predict which patients would develop frank AD (Tarkowski et al., 2003). Other researchers, taking advantage of the increased sensitivity of assaying for soluble TNF receptors rather than TNF itself, found that their levels in serum and CSF predicted, over a 4- to 6-year period, conversion to clinical AD (Buchhave et al., 2010). Some groups studied plasma levels of C-reactive protein (CRP) and α 1-antichymotrypsin (ACT) (Engelhart et al., 2004) (two acute-phase proteins up-regulated by TNF or IL-1) or of CRP alone (Laurin et al., 2009; Schuitemaker et al., 2009) and found that these markers of inflammation were present in serum and CSF before any indications of increased A β .

These studies on the primary role of inflammatory mediators have now been extended by a report that plasma levels of another acute-phase protein, clusterin (apolipoprotein J), are intimately associated with onset, progression, and severity of AD (Thambisetty et al., 2010). A novel proteomic neuroimaging paradigm was employed. Unfortunately, the authors offered only an A β -based rationale for these findings and did not note that clusterin is an acute-phase protein (Hardardóttir et al., 1994). Therefore, it is a marker, as surely as are CRP and ACT, of increased pro-inflammatory cytokines such as TNF and IL-1. One of their more telling findings was that clusterin is raised 10 years earlier in the course of the disease than is fibrillar A β deposition. Moreover, a metastudy has determined that *CLU*, the clusterin gene, is the second highest of a list of the 15 top-rated genes linked to AD on the Alzgene web-based collection (Ol-

giati et al., 2011). Taken together, these arguments are consistent with the key nature of inflammation in AD onset. The induction of insulin resistance, accepted for years by the wider literature to be mediated by TNF (see section V.D), is, like TNF, also a very early event in AD, even preceding the onset of minimal cognitive impairment (Baker et al., 2011). Indeed, insulin resistance has been reported to be associated with reduced executive function in older people lacking any evidence of T2DM or dementia. The concept of age-related cytokine increase driving this insulin resistance was one of the possibilities the authors considered (Abbatecola et al., 2004).

IV. Tumor Necrosis Factor, Amyloid β , and τ

With more than 30 years of dominance of the AD literature by amyloid β precursor protein (A β PP) and its cleavage product, A β , it is not surprising that most pathologic conditions associated with AD, including insulin resistance, have been seen as consequences of A β deposition (Balaraman et al., 2006; Perry et al., 2007; Townsend et al., 2007; Li et al., 2010; Lei et al., 2011). However, current clinical trial outcomes are consistent with A β being little more than a marker for more relevant events (Holmes et al., 2008; Green et al., 2009; Salloway et al., 2009; Extance, 2010).

Unfortunately, the direction of AD research has a momentum that has not yet, on the whole, taken into account that A β is a highly TNF-dependent protein. For instance, A β PP, the centerpiece of the amyloid theory of AD pathogenesis, is induced by inflammatory cytokines, including TNF and IL-1. This is a widespread phenomenon. In addition to the fact that the promoter region of the *A β PP* gene is controlled by these cytokines (Ge and Lahiri, 2002), its induction by these inflammatory cytokines is reported in endothelial cells (Goldgaber et al., 1989), skeletal muscle (Schmidt et al., 2008), and 3T3 L1 adipocytes (Sommer et al., 2009) as well as brain (Brugg et al., 1995; Buxbaum et al., 1998). Its presence in brain is not confined to noninfectious diseases, being described in AIDS dementia (Stanley et al., 1994) and cerebral malaria (Medana et al., 2002). Regarding A β PP cleavage, in 2004 it was reported that IFN- γ , IL-1 β , and TNF specifically stimulate α -secretase activity, with an accompanying increased production of A β (Liao et al., 2004). IFN- γ and TNF were subsequently shown to enhance A β production from A β PP-expressing astrocytes and cortical neurons, and the numbers of astrocytes expressing IFN- γ were shown to have increased (Yamamoto et al., 2007). This group also showed that 1) TNF directly stimulates β -site A β PP-cleaving enzyme (or β -secretase) expression and thus enhances β -site processing of A β PP in astrocytes and 2) that TNFR1 depletion reduced β -site A β PP-cleaving enzyme activity, as well as learning and memory deficits (Yamamoto et al., 2007). Taken together, these data imply that anti-TNF agents should be effective A β PP cleavage inhibitors.

Data from a mouse AD model after long-term inhibition of TNF are functionally consistent with this (McAlpine et al., 2009).

In contrast, it now seems reasonably appreciated that inflammatory cytokines such as TNF mediate events downstream of $A\beta$. Nearly a decade ago TNF was reported to alter synaptic transmission in hippocampal slices (Tancredi et al., 1992). Several years later (Wang et al., 2005b; Rowan et al., 2007), it was shown that this earlier observation explained the ability of $A\beta$, through TNF, to do the same. Other researchers expanded the roles of TNF in this context (Pickering et al., 2005; Stellwagen et al., 2005). The capacity of $A\beta$ to act as a ligand for CD14 and toll-like receptor-2 (Fassbender et al., 2004; Jana et al., 2008; Tükel et al., 2009) indicates that these findings with $A\beta$ (Wang et al., 2005b; Rowan et al., 2007) are consistent with basic immunology, because occupancy of CD14 and toll-like receptors is how the usual bacterial- and protozoal-origin inducers of TNF operate (Beutler and Poltorak, 2001). Key support for this concept has been provided by the recent demonstration that the release of proinflammatory cytokines from astrocytes is necessary for either $A\beta$ to be neurotoxic or τ phosphorylation to be initiated (Garwood et al., 2011). Much research on $A\beta$'s causing the pathological features of AD (Hardy and Selkoe, 2002; Games et al., 2006; Marwarha et al., 2010) appears yet to take this body of literature into consideration. In short, it should by now be clear that many experimental observations attributed to added $A\beta$ might well actually be caused by the inflammatory cytokines, including TNF. This additional TNF may have added to the total load (Fig. 1), but if it were a significant contributor to the clinical outcome, we would expect the human trials of anti-amyloid therapies discussed earlier to have given positive results.

Likewise, hyperphosphorylated τ , another histological sign of high cytokine activity (Medana et al., 2005, 2007; Gorlovoy et al., 2009) can be regarded as one of the obvious markers of GSK-3 (see section VI) activation subsequent to cytokine-induced insulin resistance, rather than as an essential early step in the pathogenesis of the disease. Hyperphosphorylated τ has been advocated for many years as a primary mechanism of loss of cerebral function and cell loss (Goedert, 2004; Götz et al., 2012), and mice expressing mutant human τ are reported to exhibit many of the features of AD (Takeuchi et al., 2011). However, claims for a direct harmful effect on neurons need to be reconciled with evidence of a large reversible increase in hyperphosphorylated τ , leaving function and structure able to return unscathed once experimentally induced mammalian hibernation is reversed (Härtig et al., 2007). Conceivably this particular phosphorylation, although spectacular down a microscope, may well be the least important of the myriad of other, unseen, phosphorylations caused by GSK-3 activation. In summary, we argue that the now-

known complexities of the current literature on the cytokines, insulin resistance, and GSK-3 reduce the need for incorporating the traditional AD hallmark proteins, however histologically intriguing, into our model to understand the origins and mechanism of this disease.

V. Insulin

A. Insulin in Basic Biology and the Brain

Over the decades, the literature of soluble mediators referred to as cytokines or hormones (conceivably interchangeable terms) have taken unexpected turns, typically through the discovery of functions quite unrelated to those for which they first came to notice. For instance, given its original function of tumor killing (Carswell et al., 1975), it was difficult to get acceptance of any role for TNF in innate immunity or disease pathogenesis (Clark et al., 1981). Insulin receptors had already been noted to be widely distributed in the central nervous system of the rat (Havrankova et al., 1978). This unexpected information was soon followed by reports of conventional insulin and insulin receptors in flies, earthworms, and bacteria (LeRoith et al., 1981a,b). The central relevance of insulin to brain physiology was a ground-breaking revelation (for review, see Adamo et al., 1989). Clearly, these and similar developments indicate that insulin has a central importance in biological signaling.

As has recently been reviewed (Correia et al., 2011), once bound to the extracellular domain of a specific tyrosine kinase receptor, insulin causes autophosphorylation of its intracellular component, triggering a chain of tyrosine kinase activity. As these authors discuss, subsequent phosphorylation activates cascades that include phosphoinositide 3-kinase/protein kinase B (Akt). This pathway (one of those inhibited by excess TNF) in turn phosphorylates and thereby inhibits (Cross et al., 1995) the α and β cytosolic forms of GSK-, which is a serine/threonine protein kinase with profound importance in many biological systems, including neurotransmission at the synaptic level (Smillie and Cousin, 2011). Other pathways, such as c-Jun N-terminal kinase/mitogen activated protein kinase, omitted here for brevity, are also involved. The phosphoinositide 3-kinase/Akt cascade also triggers translocation of the insulin-sensitive glucose transporter 4 to the cell surface, enhancing glucose uptake (Bryant et al., 2002). This is clearly central to mitochondrial function and therefore ATP production in AD. Nevertheless, there is ample evidence that insulin has the capacity to control memory independently of its effects on glucose uptake (Craft et al., 1996, 1999).

B. Insulin Resistance and Alzheimer's Disease

Insulin resistance can be regarded as 1) a decreased response in the presence of normal insulin levels or as 2) the need for more insulin for a normal response (i.e., the uptake of glucose, amino acids and fatty acid by

peripheral tissues). As far as we are aware, the first suggestions that insulin function was suppressed in AD were made more than a decade ago in the context of energy metabolism (Hoyer et al., 1994, 2000). Given the many essential roles of insulin documented in neurophysiology, the consequences of alterations in cerebral insulin resistance are inevitably widespread. This review focuses on more recent studies on the control of insulin resistance, and its implications, in a number of diseases, including AD, where it is attracting much current attention from prominent groups coming from quite different directions (Correia et al., 2011; Liu et al., 2011; McNay and Recknagel, 2011).

C. Tumor Necrosis Factor and Insulin Resistance

The basic literature that spans both immunity and metabolism accepts that pro-inflammatory cytokines cause insulin resistance, and anti-inflammatory cytokines promote insulin sensitivity (Chawla et al., 2011). Nevertheless, the implications of this link have not yet reached the AD literature, even though it dwells considerably on both inflammation and insulin resistance, two of the most recognized processes associated with the disease. Likewise, an awareness of this connection adds an important additional dimension to the literature on the pathogenesis of fetal alcohol syndrome disorder. As with AD, research on this disorder contains two fields, presently discrete, that it would be useful to conceptually merge: 1) ethanol induction of TNF in vivo (Qin et al., 2008) and in vitro (Boyadjieva and Sarkar, 2010), thus harming neurons (Boyadjieva and Sarkar, 2010; Hicks and Miller, 2011), and 2) ethanol-induced insulin resistance (de la Monte et al., 2005, 2011; de la Monte and Wands, 2010). As Fig. 1 illustrates, this would open up a wider awareness of treatment possibilities for both conditions.

The causative link between TNF and insulin resistance has a long history. In 1967, insulin resistance was observed in a patient with tularemia (Shambaugh and Beisel, 1967), a condition caused by *Francisella tularensis*, a Gram-negative tick-borne coccobacillus that much later proved to be a strong inducer of TNF and its downstream cytokines (Golovliov et al., 1996). By 1974, insulin resistance had been reported in septic and traumatized patients (Gump et al., 1974) and was generated in vivo by injecting bacterial endotoxin (Chaudry et al., 1974). This same agent was shown, in 1975, to be the prototype inducer of TNF (Carswell et al., 1975). That year also saw burn injury, recognized decades later to increase TNF to a functionally important degree (Girouir et al., 1994; Boehm et al., 2010), being reported to cause insulin resistance in rats (Frayn, 1975). The endotoxin concept of insulin resistance in sepsis was extended to skeletal (Raymond, 1984) and cardiac (Raymond et al., 1988) muscle, although with no mention of TNF or other cytokines as intermediaries. Im-

portantly, these authors proposed that a post-insulin receptor site was responsible.

In the early 1980s, after acceptance that harmful effects of bacterial endotoxin and other functionally similar agents were caused through host-origin soluble proteins (eventually termed cytokines) that were elicited from patients' cells, these proteins were linked with induction of insulin resistance. Initially, a semipurified protein that bacterial endotoxin released from macrophages was demonstrated to cause insulin resistance in adipocytes (Pekala et al., 1983). This undefined protein, in a class then termed monokines, did not affect insulin binding or stimulation of glucose uptake. Two years later it was sequenced (Beutler et al., 1985) and found, unexpectedly, to be identical to a previously sequenced molecule, TNF (Aggarwal et al., 1985). In 1989, a group who explored this area by infecting rats with *Escherichia coli* (Lang and Dobrescu, 1989) also predicted a defect in insulin signaling distal to receptor binding but again did not mention the link, by then well established, between endotoxin from this bacterium and TNF induction (Carswell et al., 1975).

A milestone article, also in 1989 (Fraker et al., 1989), demonstrated that injecting insulin and recombinant TNF concurrently into rats prevented or significantly reduced a range of metabolic and pathological changes seen in acute TNF toxicity. Various interpretations were proposed, but none proved satisfactory. With hindsight, it seems plausible that sufficient insulin had been injected to overcome much of the insulin resistance caused by the coadministered TNF. If so, the breadth of metabolic and histological observation in this text gives an intriguing insight into the wide influence of signal modification driven by cytokine-induced insulin resistance, much still unexplored. Weiner et al. (1991) found insulin and recombinant TNF to produce potent and opposing physiological signals in adipocytes. This paved the way for groups interested in various non-AD diseases, including examples caused by infectious agents known to induce TNF, to demonstrate that this cytokine was a potent cause of insulin resistance (Lang et al., 1992; McCall et al., 1992; Davis et al., 1993; Feinstein et al., 1993; Hotamisligil et al., 1993, 1996; Li et al., 2007; Qin et al., 2007; Lorenzo et al., 2008). Feinstein et al. (1993) seem to have been the first to argue that TNF exerts a major part of its antiinsulin effect by interrupting insulin-stimulated tyrosine phosphorylation, a key observation that was confirmed in cells from knockout mice by Nieto-Vazquez et al. (2007). Much of this work was done in the context of T2DM. Newer reports from within the T2DM and AD interface discuss, as one entity, the cerebral and peripheral TNF and insulin relationship (Liu et al., 2011; Bomfim et al., 2012).

Inhibiting TNF can prevent or reverse insulin resistance. Uysal et al. (1997) showed that insulin resistance did not develop in obese mice lacking TNF function. Seven years later a series of patient studies began to

appear in which commercial anti-TNF biological agents reduced insulin resistance in T2DM (Yazdani-Biuki et al., 2004), rheumatoid arthritis [in some (Kiortsis et al., 2005; Gonzalez-Gay et al., 2006, 2010, 2012) but not all (Ferraz-Amaro et al., 2011) reports], and ankylosing spondylitis (Kiortsis et al., 2005). In addition, infliximab, one of these commercial anti-TNF biological agents, was tested in obese diabetic mice, and it improved insulin signal transduction in muscle, liver, and hypothalamus. In doing so, it completely restored the activity of insulin-induced insulin receptor, insulin receptor substrate-1, and receptor substrate-2 tyrosine phosphorylation and Akt and forkhead box protein O1 serine phosphorylation (Araújo et al., 2007). In the same vein, others have reported that insulin signaling in endothelial progenitor cells, measured by the phosphorylated to total Akt ratio, was reduced by 56% on exposure to TNF (Desouza et al., 2011). Even more recently, infliximab has been employed to demonstrate that the *in vitro* insulin resistance induced by β is inhibited by neutralizing TNF (Bomfim et al., 2012).

Because treatment of AD with large anti-TNF biological agents is focused on delivering them into the CSF (section XI.B), the most AD-relevant *in vivo* demonstration to date of altering insulin resistance in this way has been done by Arruda et al. (2011), who showed that intracerebroventricular infliximab improved insulin signal transduction through insulin receptor substrate 1. This was accompanied by a whole-body reduction in insulin resistance.

D. Functional Links of Glucagon-Like Peptide-1 to Insulin Resistance

Certain gut peptides, the most prominent being GLP-1, have emerged as central to understanding both brain function (During et al., 2003) and insulin physiology. As has been reviewed in the context of neurodegenerative disease (Greig et al., 2004b; Hölscher and Li, 2010; Holst et al., 2011), GLP-1, an endogenous insulinotropic peptide, reduces insulin resistance (Cabou et al., 2008; Knauf et al., 2008). It was originally believed to arise only from L cells in the distal ileum and colon but is now intensively studied as a peptide of brain origin, with key brain functions. GLP-1 and its mimetics provide a set of signals that are the reverse of those (e.g., regarding Akt and c-Jun N-terminal kinase) generated by excess TNF (Li et al., 2005; Ferdaoussi et al., 2008; Natalicchio et al., 2010). Consequently, GLP-1 mimetics have the capacity to reduce insulin resistance in ways shared by exogenous anti-TNF agents. Because GLP-1 is rapidly degraded *in vivo*, degradation-resistant analogs have been developed and are in therapeutic use for T2DM. As discussed in section XI.F, these agents also show promise in AD models.

VI. Tumor Necrosis Factor and Glycogen Synthase Kinase-3

In the literature, GSK-3 β predominates over the very similar GSK-3 α form and, for simplicity, is referred to exclusively in this text. As with a number of other molecules with very high profiles, the fame of GSK-3 β not rests not on its first description [arising from the capacity to phosphorylate and thence inactivate glycogen synthase (Embi et al., 1980)] but on the gradual realization of its very great number of substrates, more than 50 of them documented by 2003 (Doble and Woodgett, 2003). Fifteen years earlier, TNF had caused a similar stir when, as a cytokine still traditionally linked in most minds only to tumor necrosis, it was noted to possess a remarkably high number of physiological as well as pathological functions (Nathan, 1989). We have previously discussed this in the CNS context (Clark et al., 2010). In hindsight, this information contained the potential to have opened minds to the possibility of a functional link between these two strikingly pleiotropic molecules associated with normal physiology, innate immunity, and inflammation.

As with TNF, many groups are interested in the roles of GSK-3 β in brain function. Over the years, those arguing for a primary role for hyperphosphorylated τ in AD pathogenesis have, as expected, focused on GSK-3 β as the phosphorylating kinase that generates this form of τ (Mandelkow et al., 1992; Lovestone et al., 1994; Lovestone and Reynolds, 1997). Other have examined its effects on the brain itself and produced much compelling data suggesting that GSK-3 β , in its inhibited state, is essential for normal brain function, and its activated state leads to the array of functional loss seen in AD (Jope and Johnson, 2004; Balaraman et al., 2006; Engel et al., 2006; Hooper et al., 2007; Kimura et al., 2008; Salcedo-Tello et al., 2011; Smillie and Cousin, 2011). As noted in section VI, the argument that whenever GSK-3 β activation is high, the hyperphosphorylated τ generated initiates disease (Goedert, 2004) has yet to explain the reported harmlessness of this protein in induced mammalian hibernation (Härtig et al., 2007). Certainly, the position of hyperphosphorylated τ in Fig. 1 is reinforced by the evidence that it is reduced when the tap is turned off at the top of the cascade by LH ablation (Lin et al., 2010), anti-TNF (Shi et al., 2011), IL-1 signaling blockade (Kitazawa et al., 2011), minocycline (Garwood et al., 2010), sex steroids (Carroll et al., 2007), or additional insulin (Hong and Lee, 1997).

TNF and GSK-3 β have proved to be functionally linked, both in physiology and disease pathogenesis. Insulin resistance, a phenomenon readily caused by TNF (see section V.C), has long been known to influence GSK-3 β activity (for review, see Jope 2004; Jope and Johnson, 2004). As noted above (Fraker et al., 1989), insulin also reduces the harmful effects of excess TNF production, as do sex steroids (e.g., (Jiang et al., 2009).

In addition, the reduction of endotoxin and peptidoglycan-induced pathologic conditions in rats by insulin, independent of blood glucose changes, has been demonstrated to involve GSK-3 inhibition (Dugo et al., 2006). Others reported that the insulin resistance and associated increase in GSK-3 β activity in brains of a mouse model of T2DM, as well as what the authors noted were learning difficulties parallel to those seen in AD, were corrected by administering insulin (Jolivalt et al., 2008). Moreover, the specific GSK-3 β inhibitor 3-(2,4-dichlorophenyl)-4-(1-methyl-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (SB216763) altered the cytokines released from endotoxin-stimulated human monocytes to a strongly anti-inflammatory profile (Martin et al., 2005). Nevertheless, the separation of the two in the minds of most researchers has led to the existence of both inflammatory and GSK-3 models of AD. Rarely are they discussed together, and then only in terms of post-A β secondary inflammation, not as two subunits of an essential component of disease initiation (Hooper et al., 2008).

VII. Tumor Necrosis Factor and Mitochondrial Dysfunction

As we have reviewed previously (Clark et al., 2010), the concept of dysfunctional mitochondria, and thus poor oxygen utilization and energy production, is important in understanding disease pathogenesis. This seems to have been first suggested, on the basis of organelle electron microscopy, in malaria (Maegraith, 1954). Nearly 20 years later, it appeared in the sepsis literature (Mela et al., 1972). A further 2 decades later, TNF, by then well established as a key mediator in infectious disease, was first demonstrated to suppress mitochondrial respiration (Stadler et al., 1992). By the end of that decade, extensive functional studies in this context were begun (Fink, 1997, 2000, 2001), and the general reasoning was extended to HIV dementia (Kruman et al., 1999) and influenza encephalopathy (Yokota, 2003). More recent research on TNF's ability to induce mitochondrial dysfunction (Chen et al., 2010) again noted that direct treatment with TNF led to reduced intracellular ATP and more generation of reactive oxygen species. More significantly, the anti-TNF biological agent etanercept has been shown to ameliorate cardiac mitochondrial dysfunction in vivo (Moe et al., 2004). Systemic mitochondrial dysfunction, as part of cytokine-induced inflammation, is still very topical in the pathophysiology of sepsis (Garrabou et al., 2012).

Mitochondrial dysfunction has an early onset in AD (Hauptmann et al., 2009) and is widely regarded as important in its pathogenesis (Castellani et al., 2002). Although the first group to propose mitochondrial functional defects as a mechanism for AD was primarily interested in oxidative stress as a mechanism (Blass and Gibson, 1991), it did not take long for researchers of A β , by then dominating AD disease pathogenesis, to incor-

porate the mechanism of mitochondrial dysfunction into their reasoning (Kaneko et al., 1995). This view persists to the present day (Borger et al., 2011) and has remained largely unquestioned despite the implications of the prevalence of TNF in AD brains (section III) and the widely published capacity of this cytokine to induce both A β PP and A β (section IV) and to directly cause mitochondrial dysfunction (see above). Young-Collier et al. (2012) found that the reduced expression of mRNA of genes responsible for mitochondrial function in human AD neurons could not be duplicated with 3 days of culture with A β ₁₋₄₂ (instead, expression rose); this might now encourage investigation into other possible mechanisms for the finding.

Does mitochondrial dysfunction precede or follow insulin resistance? Both viewpoints appear in the literature, with discussion of excessive fat intake being common to several articles arguing that mitochondrial dysfunction occurs first (Anderson et al., 2009; Rector et al., 2010). In contrast, a study designed to investigate the mitochondrial dysfunction during fasting concluded it was a consequence rather than a cause of insulin resistance (Hoeks et al., 2010). Indeed, when associated with cell death or apoptosis, mitochondrial dysfunction is reported to occur after GSK-3 β activation (Petit-Paitel et al., 2009; Wang et al., 2011), placing it after insulin resistance (Fig. 1). Its position here is consistent with experiments in which the mitochondrial dysfunction induced by SZT, an agent that mimics T2DM or AD (section IX.A), was corrected by administering insulin (Chowdhury et al., 2010). Clearly, this implies that improved cerebral mitochondrial function is a plausible consequence of treating AD with intranasal insulin (section XI.E; Fig. 1).

VIII. Tumor Necrosis Factor and Progenitor Cells

A. Progenitor Cells, Tumor Necrosis Factor, and Insulin Resistance

Adult neurogenesis, which is low or absent in the shrunken brains of patients with AD, is essential for normal memory formation (Clark et al., 2010). Such progenitor activity, requiring activin A (Abdipranoto-Cowley et al., 2009), is part of a normal organism-wide pattern in which such cells are controlled by a sex hormone-TNF pathway to maintain cellular homeostasis. The dynamic regulation of neurogenesis by hypothalamic-pituitary-gonadal axis hormones, including activins, gonadotropins, and sex hormones, particularly progesterones, is well established (Vadakkadath Meethal and Atwood, 2005). However, the sequence of events through which sex hormones seem to modulate TNF during control of progenitor cells is not yet known. Despite this incomplete picture, the literature to date is consistent with the idea that increased TNF induces insulin resistance, and thus GSK-3 β activation (Verhees et al.,

2011), and constitutes the major pathway in progenitor cell homeostasis.

T2DM is a good example of a disease combining chronic systemic inflammation, insulin resistance, and widespread defects in progenitor cell function. It is telling that it should both predispose to AD (Arvanitakis et al., 2004) and share cerebral insulin resistance with this condition (Liu et al., 2011). The details of the signaling deficits are also the same (Liu et al., 2011). In neurogenesis (and, as far as has been examined, a general rule in other progenitors), physiological levels of TNF and its downstream cytokines enhance proliferation, whereas supraphysiological levels inhibit proliferation (Bernardino et al., 2008). This phenomenon has been demonstrated in thymocytes (Ranges et al., 1988; Hernández-Caselles and Stutman, 1993), hepatocytes (Bour et al., 1996; Diehl and Rai, 1996), hematopoiesis (Clark and Chaudhri, 1988; Rebel et al., 1999) and, of plausible relevance to data from AD brains (Sheng et al., 2012), impaired mitochondria biogenesis (Valerio et al., 2006). The relevance of TNF-induced insulin resistance to the pathogenesis of the widespread degenerative change that characterizes chronic inflammatory diseases can be gleaned from the literature on endothelial cell progenitors (Cubbon et al., 2009; Abbas et al., 2011; Desouza et al., 2011) and thus nephropathy; muscle progenitors (Pajak et al., 2008) and thus cachexia; fibroblast progenitors (Frankel et al., 2006; Goren et al., 2006; Siqueira et al., 2010) and thus poor wound healing; cartilage progenitors (Alblowi et al., 2009; Kayal et al., 2009) and thus poor fracture repair; and erythroblasts (Tsinkalovsky et al., 2007) and thus the anemia of chronic disease. Whether the recorded protective effect of sex hormones in some of these circumstances is an independent property parallel to their ability to reduce production of TNF (He et al., 2004; Kipp et al., 2007) is a yet to be tested. We note, however, that estrogen has been reported to promote cutaneous wound healing (Campbell 2010) by means other than its anti-inflammatory mechanism. Nevertheless, the poor wound healing in rheumatoid arthritis, a condition exhibiting insulin resistance reversible by anti-TNF agents (Kiortsis et al., 2005; Gonzalez-Gay et al., 2006), has been reported to be countered by anti-TNF treatment (Shanmugam et al., 2011). Although on a small scale, this study is intriguing, because conventional wisdom, predicated on the idea that such anti-TNF treatment has the potential to suppress immunity against certain pathogens that could infect wounds, would have us expect the opposite outcome. As might be expected, elevated levels of sex steroids, such as during pregnancy or after hormonal replacement therapy, and known to suppress TNF, leads to diminished disease activity in rheumatoid arthritis (Ostensen et al., 1983; Kanik and Wilder, 2000; Islander et al., 2011). In contrast, the disease is often aggravated after parturition (Ostensen et al., 1983).

B. Clock Genes, Controlled by Tumor Necrosis Factor, Govern Progenitor Activity

The control of progenitor cells homeostasis by TNF is but a small part of the broader control that tissue clocks exert in all tissues through circadian, or clock, genes. Indeed, cell division in general is under their control (Matsuo et al., 2003). Likewise, the normal diurnal cycles in food intake, sleep, insulin requirements, and mitochondrial function, kept in their normal circadian patterns when these genes remain under physiological diurnal fluctuations of sex hormones, TNF and downstream cytokines (Kohsaka and Bass, 2007), run amok in well documented ways during illness (Hart, 1988; Bluthe et al., 1994; Dantzer and Kelley, 2007). For as long as TNF and IL-1 β are in pathological disease-induced excess, clock genes undergo a longer-term suppression (Cavadini et al., 2007). Hence mechanisms governed by clock genes, including cell cycling (Matsuo et al., 2003), can be expected to undergo pathological change. Several years ago we proposed that such suppression can explain the pattern of pathology that characterizes severe bacterial, protozoal, viral and post-trauma disease (Clark et al., 2008).

Among the clock genes suppressed by excess TNF and IL-1 β are the period genes, *Per1*, *Per2* and *Per3* and the central, interconnecting, response element clock gene, *rev-erba* (Cavadini et al., 2007). The existence of an essentially parallel literature on reproductive hormones and clock genes (Nakamura et al., 2008; Nakamura et al., 2010; Karatsoreos et al., 2011) again demonstrate the present minimal awareness of the functionally important adjacent positions of sex hormones and TNF in the same regulatory pathway. Certain clock genes have been demonstrated to undergo insulin-dependent regulation (Tahara et al., 2011), and to control adult neurogenesis, including in the hippocampus (Moriya et al., 2007; Borgs et al., 2009; Kimiwada et al., 2009), as well as endothelial cell (Wang et al., 2008) and cartilage (Mengatto et al., 2011) progenitors. Of particular relevance here are the data from experiments published in 2004 (Kuriyama et al., 2004) in which the normal circadian clock oscillation, present in all tissues, was examined in heart and liver of mice in which diabetes was generated with SZT. *Per2* was diurnally inhibited, but this could be corrected by injecting insulin, i.e., by overcoming insulin resistance. This is consistent with glucagon-like peptide-1 (GLP-1) mimetics, clinically useful against T2DM because of their ability to correct insulin resistance (see next Section), promoting neurogenesis in AD models (Hamilton et al., 2011; Holst et al., 2011). Predictably (Jope and Johnson, 2004), the degree of activation of GSK-3 β proves to be what ultimately controls the clock genes, and thus proliferation (Hirota et al., 2008; Ko et al., 2010; Kozikowski et al., 2011). Again as expected, phosphorylation of GSK-3 β itself normally un-

dergoes robust circadian oscillation, and it readily phosphorylates *Per 2* (Iitaka et al., 2005).

Taken together, the wider progenitor cell literature is therefore consistent with inhibition of neurogenesis in AD by excess brain TNF through a pathway that involves inhibition of clock genes by insulin resistance, thus damping down or switching off progenitor cells. Evidence also incriminates chronic inflammation in reduced recruitment of new neurons into the hippocampal networks that underlie memory consolidation (Belarbi et al., 2012a). Inhibited neurogenesis and distorted cell cycling (Yang and Herrup, 2007) in AD are but two consequences of this widely applicable principle in disease pathogenesis. Logically speaking, AD is therefore susceptible to treatment with any of the approaches discussed herein that rectify insulin resistance. Moreover, the main stages of this pathway are recognized general principles as much at home in physiology [e.g., in the metabolic shutdown of hibernation (Stieler et al., 2011) and dauer, or suspended animation, forms of the nematode *Caenorhabditis elegans* (Tissenbaum and Ruvkun, 1998; Forsythe et al., 2006)] as in other human diseases beyond AD and T2DM, including stroke (Valerio et al., 2011) and depression (Li and Jope, 2010) (Fig. 2). These last two conditions have an emerging literature on therapy with anti-TNF biological agents (Uguz et al., 2009; Tobinick, 2011).

IX. Streptozotocin

A. Streptozotocin Model for Diabetes and Alzheimer's Disease

SZT, originally isolated from *Streptomyces achromogenes* for use as an antibiotic (Vavra et al., 1959), was later realized to be a potent diabetogenic agent (Junod et al., 1967); since then, it has had an important role in diabetes research. In 1983, awareness developed that

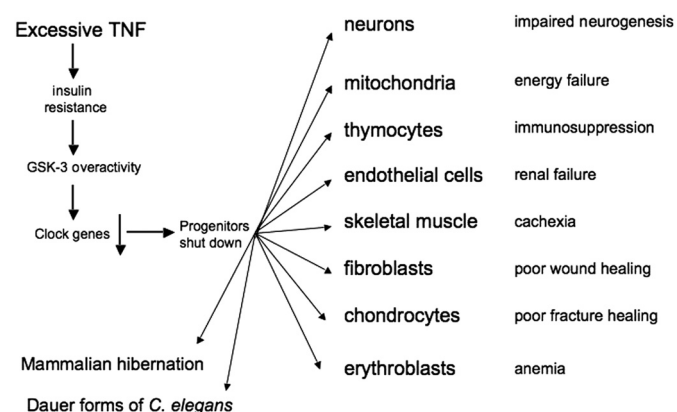


FIG. 2. The TNF-induced pathway leading to inhibition of progenitor cells. The first two cell types listed are relevant to conditions such as Alzheimer's disease, where excess TNF production is largely restricted to the brain, and all the cell types listed can be expected to be relevant to T2DM and severe systemic disease. As discussed and shown, these principles are manifest in the physiology of mammalian hibernation and the dauer forms of *C. elegans*.

SZT, besides leading to pancreatic β -cell destruction, also inhibits metabolic responsiveness to insulin rather than its binding to its receptor (Hansen et al., 1983). A decade later it was appreciated that intracerebroventricular injection of SZT produces changes in glucose metabolism that parallel those seen in AD (Plaschke and Hoyer, 1993); subsequently, its ability to bring about a wide range of the rest of the changes seen in AS began to be uncovered. For example, rats receiving intracerebroventricular injections of SZT, which does not alter systemic glucose metabolism, develop insulin receptor defects and thus insulin resistance (Hoyer et al., 2000). They also exhibit brain atrophy, neurodegeneration, gliosis, and increased immunoreactivity for activated GSK-3 β and hyperphosphorylated τ , as observed in AD (Lester-Coll et al., 2006). This model is seen as increasingly important because, in contrast to genetically generated mouse strains that dominate the experimental literature, it closely resembles the most common human condition, termed sporadic AD. There is now a considerable literature on the use of SZT to establish models of insulin resistance (Blondel and Portha, 1989; Koopmans et al., 2006; Cheng et al., 2010; Thackeray et al., 2011). As reviewed previously (de la Monte and Wands, 2008), these SZT-induced changes could be reduced or prevented by early treatment with peroxisome proliferator-activated receptor agonists in doses smaller than routinely used to treat diabetes type 2. TNF down-regulates certain peroxisome proliferator-activated receptor receptors (Beier et al., 1997).

B. Streptozotocin Induces Tumor Necrosis Factor

The capacity for SZT to induce TNF has been documented since the mid-1990s (Sagara et al., 1994; Herold et al., 1996). Cai et al. (2011) reported that it increases TNF and IL-1 β in rat hippocampus. This activity of SZT to induce TNF has been exploited to help understand the consequent pathologic features of diabetes (Sagara et al., 1994; Holstad and Sandler, 2001; Zauli et al., 2010; Devaraj et al., 2011). Specific examples include diabetic cardiomyopathy (Westermann et al., 2007) and diabetic nephropathy (Mensah-Brown et al., 2005; Navarro et al., 2005). In the latter, successful experimental treatments include combined insulin (overcoming insulin resistance) and curcumin [reducing the inflammatory response (Sharma et al., 2007)] as well as curcumin alone (Soetikno et al., 2011). A commercial anti-TNF biological agent has also been used, to good effect, for this purpose (Yamakawa et al., 2011). As far as we are aware, Isik et al. (2009) are the only researchers to use an anti-inflammatory approach (curcumin) to rationalize post-SZT insulin resistance. As might be expected from the interplay between reproductive hormones and TNF, sex steroids are well recognized to reverse post-SZT insulin resistance and protect from insulin resistance in rats exhibiting SZT-induced diabetes (Coleman et al., 1982; Ordonez et al., 2008). Surprisingly, the consensus from

this literature (i.e., that neutralizing excess TNF is a logical step in alleviating pathologic features of diabetes) has yet to translate across to research that uses SZT to duplicate AD. This should prove to be an excellent model in which to develop a close laboratory-based understanding of the effects of anti-TNF agents and sex hormones in this disease.

X. The Broader Picture—Stroke, Traumatic Brain Injury, and Infectious Disease

This review focuses on the pathogenesis of AD, with some reference to T2DM, but the gist of the pathway we have constructed (Fig. 1) evidently extends to understanding other encephalopathies in which cerebral TNF is increased by routes with current explanations other than LH/FSH (Section II). Stroke, traumatic brain injury (TBI), and brain involvement in malaria, a systemic infectious disease, are examples (Fig. 3). As summarized by Simpkins et al. (2009), AD, stroke and TBI tend to become one syndrome with the passage of time since onset. Moreover, TBI is often seen and postcerebral malaria syndrome is usually seen (Boivin et al., 2007; Kihara et al., 2009; Idro et al., 2010) in the young, before reproduction or menopause.

Induction of TNF in the penumbra of brain ischemia, the area surrounding the region worst affected by the vascular obstruction, involves glutamate and nuclear factor- κ B (Kaushal and Schlichter, 2008) and is inhibited by regulatory T cells (Liesz et al., 2009). Cerebral ischemia has also been reported (Wen et al., 2004a) to induce aberrant neuronal cell cycle re-entry that can be reduced by 17 β -estradiol, an inhibitor of TNF (Hsu et al., 2000), a cytokine with a long history of interfering with mitosis (Darzynkiewicz et al., 1984) and more recently demonstrated to cause aneuploidy (Wu et al., 2011), the phenomenon that sets the scene for aberrant cell cycling and thus apoptosis. As recently reviewed by Clark et al. (2010), trauma triggers release of inflammatory cytokines through the action of mitochondrial DNA

set free from disrupted cells (Zhang et al., 2010). In infectious diseases, much evidence exists for the direct induction of TNF by products of the pathogen, beginning with the example of bacterial lipopolysaccharide in the original TNF article (Carswell et al., 1975). For instance, ample evidence exists for the malaria toxin as a TNF inducer (Bate et al., 1989; Tachado and Schofield, 1994). As with AD and T2DM, insulin resistance is documented in stroke (Calleja et al., 2011), TBI (Mowery et al., 2009; Ley et al., 2011), and cerebral malaria (Eltahir et al., 2010b). Likewise, A β and hyperphosphorylated τ , the proteins widely regarded as AD hallmarks and appreciated to be indicators of chronically high TNF (section IV) and GSK-3 hyperactivation induced by insulin resistance (section VI), respectively, are also present in stroke (Irving et al., 1996; Nihashi et al., 2001; Wen et al., 2004b), TBI (Irving et al., 1996; Smith et al., 2003; Tran et al., 2011), and cerebral malaria (Medana et al., 2002, 2005).

Before expanding on the encephalopathies of system infectious diseases, we recall the proposal that the A β induced in AD (Bowen et al., 2004) and deposited in the cerebrovasculature is a response, albeit sometimes an insufficient one, to seal these vessels to minimize blood-brain barrier (BBB) breakdown (Atwood et al., 2002; Atwood, 2010). These arguments, developed in part to explain the neuroinflammatory reaction frequently observed during normal aging (Wilson et al., 2008), provide a plausible novel amyloid-based degree of complexity to the development of the BBB changes commonly seen in the encephalopathies of infectious disease. For instance, this reasoning plausibly applies to the A β PP present in cerebral malaria brains (Medana et al., 2002). In addition, the antimicrobial properties of its cleavage product, A β (Soscia et al., 2010), can be expected to minimize secondary bacterial invasion (a common problem in malaria because of immunosuppression) at this critical location. The association of BBB lesions with TNF generated by infectious agents is already in place in the encephalopathies associated with sepsis (Alexander et al., 2008), trypanosomiasis (Quan et al., 1999; Kristensson et al., 2010), malaria (Adams et al., 2002) influenza (Ichiyama et al., 1996), and AIDS (Mastroianni et al., 1990; Nolting et al., 2009).

Research on cerebral insulin resistance and GSK-3 activation is sparse regarding the encephalopathies of infectious disease, although some publications link systemic insulin resistance with poor cognitive performance in women infected with HIV (Valcour et al., 2012) and fatal malaria with cerebral symptoms (Eltahir et al., 2010a).

XI. Therapeutic Implications

A. Specific Inhibition of Tumor Necrosis Factor

The obvious way to capitalize on the relationship between inflammation and insulin resistance is to specifi-

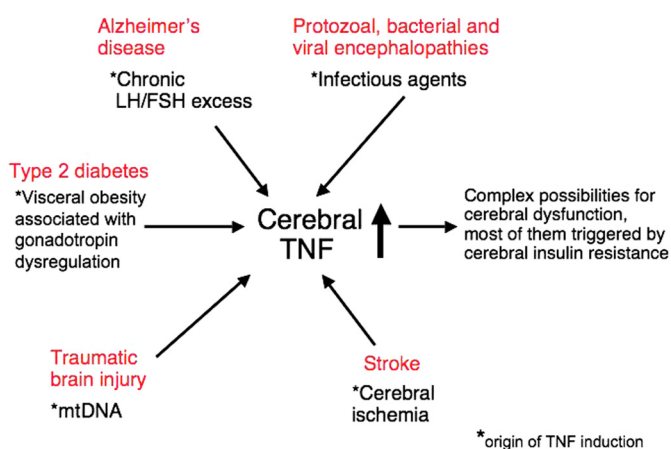


FIG. 3. Examples of the range of different inducers, in different diseases, that can lead to increased cerebral TNF and thence clinically similar outcomes.

cally neutralize excessive TNF, as is widely recognized to be useful in a number of systemic, but not cerebral, inflammatory diseases. Clearly, this limitation is imposed by the large molecular size of current therapeutically successful specific anti-TNF biological agents, such as infliximab and etanercept, which precludes their passage through the blood-brain barrier when administered subcutaneously or intravenously. Indeed, a negative result (a small 24-week double-blind trial) with subcutaneous etanercept against AD has been reported (Bohac et al., 2002), as has a positive mouse intracerebroventricular injection trial, albeit measuring only the indirect indicator A β (Shi et al., 2011). Because the intracerebroventricular route is a precarious one, unsuited to regular administration to the same patient, a number of ways to circumvent this problem are being developed to widen the use of these highly successful biological agents to a new patient group. The earliest of these is a novel approach termed the perispinal route (Tobinick et al., 2006, 2010, 2012). Its logic depends on 1) a short period of head-down tilting to gain a gravitational advantage, 2) an awareness of anatomy of Batson's plexus [a valveless venous system that surrounds the spinal column in continuum with the choroid plexus (Nathoo et al., 2011)], and 3) knowledge of the effect of acute hypertension on choroid plexus permeability [a 30-fold increase in albumin in CSF within 10 min of pharmacologically induced acute local hypertension (Murphy and Johanson, 1985)]. Not surprisingly, therefore, the gravitational effect on this valveless blood column of a 5-min head-down tilt of head and trunk has been reported, in anesthetized rabbits, to increase dramatically the passage of albumin and globulin, molecules of etanercept size, from plasma to the cerebrospinal fluid (Wen et al., 1994). The authors noted that this would be a useful way to get large molecules into the CSF for therapeutic purposes.

The apparent indifference of the makers of etanercept to the claims of the perispinal anti-brain TNF approach to treating AD (Tobinick et al., 2006; Tobinick and Gross, 2008) has not deterred other investigators from aspiring to the same outcome by several approaches. One group is developing what it refers to as a molecular Trojan horse decoy receptor system to get a similar anti-TNF fusion molecule into the brain (Pardridge, 2010; Zhou et al., 2011). Others (<http://www.neurokine.com/index-3.html>) employ encapsulation of etanercept in liposomes, a well recognized technology (Paolino et al., 2011), to get the same result. It is encouraging that this web site notes Dr. Patrick McGeer, a long-time exponent of earlier approaches to minimizing brain inflammation (McGeer and McGeer, 1995), as a consultant. Another approach under way is to devise anti-TNF nanoantibodies small enough to pass the BBB (Harmsen and De Haard, 2007; Vandenbroucke et al., 2010).

It warrants noting here that the dual activity of TNF as a component of innate immunity and disease patho-

genesis has made it inevitable that certain infections, particularly tuberculosis and those caused by certain protozoa, have a tendency to be exacerbated during long-term anti-TNF therapy. This has been comprehensively reviewed (Clark et al., 2010). The very extensive use of this treatment in a number of inflammatory diseases, particularly rheumatoid arthritis, demonstrates that this challenge can be managed successfully.

B. Nonspecific Inhibition of Tumor Necrosis Factor

1. *Thalidomide and Curcumin.* Brain TNF levels can also be diminished therapeutically by thalidomide (Alkam et al., 2008; Ryu and McLarnon, 2008) or its derivatives (Greig et al., 2004a; Tweedie et al., 2007; Belarbi et al., 2012b), and current research programs are examining this in an AD context. Likewise, curcumin, a long-appreciated inhibitor of TNF (Chan, 1995), is used for this purpose in its original form (Cole et al., 2007) as well as more effective (i.e., in terms of brain entry) derivative forms (Chiu et al., 2011; Tsai et al., 2011). All of the authors whose work is cited in this section might have unwittingly been improving insulin signaling as well as achieving their stated aims, but this remains unexplored. The exception appears to be Iisik et al. (2009), who employed the anti-inflammatory activity of curcumin to examine its effects on both insulin resistance and memory in a rat model of SZT-induced AD. Curcumin is also reported to protect testosterone-producing Leydig cells and pancreatic cells from toxicity (Giannessi et al., 2008).

2. *Minocycline.* Minocycline is a particularly broad-spectrum oral tetracycline that was synthesized from a naturally occurring antibiotic decades ago (Church et al., 1971). Being the most lipid-soluble of this class of drug, it enters the brain more readily than the rest. Although not without side effects, it has been known for 15 years to be anti-inflammatory in vivo (Tilley et al., 1995), and its avid brain penetration is responsible for the attention it has received in the neuroinflammation literature (Peng et al., 2006). It is often termed an inhibitor of microglial activation, and the list of inflammatory cytokines it down-regulates, in brain and elsewhere, includes TNF and IL-1 β (C  lerier et al., 1996; Lee et al., 2004; Suk, 2004; Wang et al., 2005a). Consistent with the overarching pathway central to this review, minocycline shows experimental promise as a treatment, complementary to the others we discuss, for the various manifestations of excess production of these cytokines in the brain (Familiari et al., 2006; Seabrook et al., 2006; Choi et al., 2007; Fan et al., 2007; Noble et al., 2009). A human AD trial with minocycline is under way (<http://clinicaltrials.gov/ct2/show/NCT01463384>).

3. *Erythropoietin.* Another endogenous humoral factor, these days referred to as a cytokine but described decades before this term was in use, is erythropoietin (EPO). It was discovered as a hormone that drives erythropoiesis and thus provides the means to deliver more

oxygen to tissues. Apart from its large-scale clinical use in treating chronic anemias, it gained notoriety as a performance-enhancing drug, in due course an illegal one, in sports. EPO warrants mention in this section because it has proved to be extremely pleiotropic, in retrospect probably because of its capacity to inhibit nuclear factor κ B-inducible pathways (Nairz et al., 2011). It has been reported for many years to have protective roles in stroke and traumatic brain injury (for review, see Sargin et al., 2010; Chateauvieux et al., 2011; Nairz et al., 2012; Sølling, 2012), and it is referred to as a multifunctional tissue-protective cytokine. EPO is also on record as enhancing neurogenesis (Osredkar et al., 2010), oligodendroglial progenitors (Kim and Jung, 2010), endothelial progenitors (Xu et al., 2011), and mitochondrial biogenesis (Carraway et al., 2010). It has the potential to inhibit cell-mediated immunity as well as disease (Nairz et al., 2011), as can anti-TNF treatment (Mayordomo et al., 2002). Hippocampal memory is also reported to be enhanced in mice treated with EPO for 3 weeks (Adamcio et al., 2008).

All of these phenomena have TNF mirror images in the literature, sometimes discussed in terms of the insulin resistance TNF induces (Meistrell et al., 1997; Valerio et al., 2006; Alkam et al., 2008; Bernardino et al., 2008; Cubbon et al., 2009; Chio et al., 2010; Chen et al., 2011). Thus, the concept of endogenous anti-TNF activity being one of the biological roles of EPO is very plausible, as is harnessing this attribute for disease therapy. Unfortunately, the long history of indifferent recombinant EPO trials in disease has been clouded by a propensity for its erythropoietic properties to dominate, with a sometimes fatal thrombosis a feature of its chronic use (Patel et al., 2011a). Thus nonerythropoietic variants of this molecule are being developed. They fall into two main categories: carbamylated EPO (Ramirez et al., 2009; Leconte et al., 2011) and nonerythropoietic tissue-protective proteins that mimic the three-dimensional structure of EPO, such as pyroglutamate helix B-surface peptide (Patel et al., 2011b). Hand and Brines (2011) and Sølling (2012) have reviewed this area. Information such as toxicity and efficacy within the wide range of activities of native EPO is still being gathered for these variants.

The retarded neurogenesis seen in infection with Japanese encephalitis virus has been reported to be reversible by abrogating the inflammatory response of microglia, including TNF production, with exposure to minocycline (Das et al., 2011). Protection against simian cerebral pathologic conditions related to HIV by minocycline has also recently been recorded (Ratai et al., 2010; Campbell et al., 2011). Therefore, it warrants testing whether all of the above reasoning applies to possible treatments for the encephalopathies of systemic infectious disease.

As noted above, malaria comes into the category of systemic inflammatory diseases that may develop an

associated encephalopathy. This condition in children in tropical Africa is also noteworthy for a well documented AD-like syndrome that can follow acute cerebral symptoms, despite recovery from systemic disease. This syndrome correlates with CSF levels of TNF and exhibits long-term cognitive impairment, including deficits in memory, attention, visuospatial skills, language, and executive function (Carter et al., 2005; Boivin et al., 2007; John et al., 2008a,b; Kihara et al., 2009). This condition is also noted for aggressive behavior (Idro et al., 2010), as is AD (Ballard and Walker, 1999). We have reviewed the literature linking TNF with aggression (Clark et al., 2010). Researchers were alerted to the possible implications of the tissue-protective aspects of EPO in malaria through evidence that its recombinant form lowered TNF levels and prevented cerebral complications and death in a mouse model of the disease (Kaiser et al., 2006). Raised serum levels of EPO have been reported to be associated with a lower incidence of neurological sequelae in Kenyan children infected with malaria (Casals-Pascual et al., 2008), leading to the suggestion of using this cytokine therapeutically to protect against brain damage (Casals-Pascual et al., 2009). Although a short-term open trial in Mali showed no increased mortality (Picot et al., 2009), others (John et al., 2010) have pointed out the limited opportunity to detect thrombotic side effects, the chief concern in the wider literature (Patel et al., 2011a), on using unaltered erythropoietin. Meanwhile, there appears to be a consensus (Casals-Pascual et al., 2009; John et al., 2010) to await the outcome of basic studies of the EPO variants discussed earlier (Hand and Brines, 2011; Leconte et al., 2011; Patel et al., 2011b). Some of the potentially less damaging approaches depicted in Fig. 1, such as oral minocycline or inhaled insulin, could be considered in the meantime. Nevertheless, we regard EPO variants as exciting future prospects for therapeutically addressing the overarching pathway developed in this review.

C. Administering Leptin As a Counter to Insulin Resistance

Clark et al. (2011) summarized the literature on leptin and TNF having mirror image effects on AD. As noted, administering additional leptin and lowering TNF levels are both on record as improving memory and learning, reducing anxiety, lowering A β and hyperphosphorylated τ , reducing β -secretase activity, increasing dendritic spine growth, activating GSK-3, and activating AMP kinase-activated, pentylenetetrazole-induced seizures. As we noted (Clark et al., 2011), this pattern had previously escaped recognition. A case for the centrality of insulin resistance in AD is further strengthened by the opposite effects on insulin resistance of leptin (German et al., 2010; Koch et al., 2010) and TNF, leptin reducing and TNF increasing it.

Leptin may also have additional direct effects on neurons as an antiapoptotic, proneurogenic adipokine (Paz-

Filho et al., 2010b), and its administration to leptin-deficient humans has altered brain function and increased gray matter (London et al., 2011). Leptin is currently administered in other diseases, such as lipodystrophy syndromes, hypothalamic amenorrhea, and nonalcoholic steatohepatitis, but its CNS effects have not yet been thoroughly evaluated. Its endogenous levels have been negatively correlated with the risk of developing AD in lean (leptin sensitive) but not obese (leptin insensitive) older people (Lieb et al., 2009), implying that only lean people would be susceptible to treatment with leptin (Paz-Filho et al., 2010a).

Neither leptin nor anti-TNF agents yet appear to have been tested against the SZT model of AD, although leptin reduces insulin resistance (Lin et al., 2002) and leptin deficiency increases it (German et al., 2011), in the SZT model of T2DM. Because normal insulin sensitivity keeps GSK-3 β activity low, administering leptin should also decrease its activation and τ hyperphosphorylation. This, too, has also been reported in neurons (Greco et al., 2009). The ability of leptin to increase insulin sensitivity has yet to be explored as an explanation for the novel observation that intracerebroventricular injection of leptin dramatically, albeit briefly, improves a wide range of pathologic features in a mouse model of type 1 diabetes (Fujikawa et al., 2010). The systemic improvements recollect those achieved, as discussed earlier, with intracerebroventricular injections of infliximab, a commercial anti-TNF biological agent (Aruda et al., 2011).

D. Administering Insulin As a Counter to Insulin Resistance

Interest in this approach to treating AD appears to have arisen when it was realized that the temporary memory improvement in patient brain function after systemic administration of insulin was independent of the attendant serum glucose concentration (Craft et al., 1996, 1999). Evidently, more subtle pathways are at work. Others found that the effects of intranasal insulin could alter basic central nervous system function in euglycemic healthy volunteers (Kern et al., 1999) and a few years later documented the changes in CSF levels of insulin so caused, as well as the absence of systemic changes in insulin or glucose (Born et al., 2002). By 2004 (Benedict et al., 2004), they had reported improvements, in a similar group of healthy volunteers, in memory and mood after 8 weeks of treatment. Soon after, another group reported a pilot trial that exhibited memory improvement after this treatment in patients with AD (Reger et al., 2006). They also reported, then and subsequently (Reger et al., 2008), that responses were absent, under the conditions tested, in apolipoprotein E (apoE)4-positive patients. Given that a major controller of insulin resistance is the inflammatory cytokine TNF (see section V.C), it is important, when considering possible reasons for this difference, to take into account the in-

teractions between apoE4⁺ and TNF. One study of possible relevance, as yet unexplored, concerns the inflammatory status of microglia (and thus effects on insulin resistance, although this was not in their protocol) from mice expressing different numbers and types of human apoE genes (Vitek et al., 2009). This is discussed further in section XI.H.

Ott et al. (2012) discussed the pitfalls and potential of intranasal insulin administration on cognitive function in general, and Ketterer et al. (2011) focused on possible ways, through new insulin analogs, such as aspart and detemir, to optimize reduction of cerebral insulin resistance. Subsequently, Benedict et al. (2012) and Schiöth et al. (2012) documented an association between impaired insulin resistance with deficits in verbal fluency and temporal lobe gray matter volume in the elderly and evaluated the therapeutic potential of reversing this resistance with intranasal insulin. The former of these publications is reminiscent of the association observed between insulin resistance and executive function (Abbatecola et al., 2004).

E. Glucagon-Like Peptide-1 Mimetics and Dipeptidyl Peptidase-4 Inhibitors As Counters to Insulin Resistance

Being rapidly degraded (minutes) in vivo by DPP-4 (see section V.E), native GLP-1 is impractical as a therapy. Hence, degradation-resistant GLP-1 receptor agonists, often termed GLP-1 mimetics, have been developed (Ahrén, 2011a,b), and a number of these agents are in therapeutic use subcutaneously in T2DM. Exenatide is an example from a group of drugs based on exendin-4, a GLP-1-like molecule isolated from a reptile. Another approach, based on synthesizing GLP-1 analogs, has led to other subcutaneous agents, such as liraglutide (Buse et al., 2009). Both of these types of GLP-1 mimetics pass through the blood-brain barrier and have proved to be strikingly active against AD models (Perry et al., 2003; Liu et al., 2009; Porter et al., 2010; Li et al., 2011; McClean et al., 2011) as well as against a model of the cognitive defects in T2DM (Gault et al., 2010). Recent basic studies give impressively detailed reinforcement to this approach (Bomfim et al., 2012; Talbot et al., 2012). In addition, a number of agents have been developed, such as sitagliptin, which inhibits the catalytic site of DPP-4 (Ahrén and Foley, 2008; Ahrén, 2009) to extend the life of endogenous GLP-1. They are marketed for treating T2DM and have the practical advantage of being administered orally, although their testing in AD models remains in its infancy (D'Amico et al., 2010).

F. Glycogen Synthase Kinase-3 Antagonists

SB216763, presumably tested for its effects on endotoxin-treated human monocytes (Martin et al., 2005), showed a degree of promise in a model of AD generated by injecting an A β oligomer into aged rats but made outcomes worse in control rats (Hu et al., 2009). As this group suggested, less

potent inhibitors that do not inhibit constitutional GSK-3 may be necessary. The study by Engel et al. (2006) is consistent with this. In terms of lowering phosphorylated τ levels and decreasing spatial memory loss, others successfully tested a GSK-3 inhibitor, a thiadiazolidinone termed 4-benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione (NP12), in a transgenic mouse model of AD (Serenó et al., 2009). However, the mice did not live longer. 2-Methyl-5-(3-[4-[(S)-methylsulfinyl]phenyl]-1-benzofuran-5-yl)-1,3,4-oxadiazole, another novel GSK-3 inhibitor, has recently been reported to produce a similar positive outcome in vitro and in a mouse model (Onishi et al., 2011). Successfully targeting GSK-3, now a goal in many disease fields, is evidently a complex undertaking. Engagingly, cardiac researchers have referred to the challenge it presents as a very sharp double-edged sword (Cheng et al., 2011). This approach, as well as those discussed in the rest of this section, is shown in Fig. 1. The major treatment concepts and their intended or predictable consequences are collected in Table 1.

H. Apolipoprotein E Mimetics and Bexarotene

As reviewed by Laskowitz et al. (2001), the protein apoE was identified by its role in the transport and metabolism of cholesterol and triglycerides. It is the major apolipoprotein generated in the brain, where it originates from glial cells. Human genetic variation accommodates three isoforms: apoE2, apoE3 (the most common), and apoE4. In brief, the more apoE4 generated, the less functional apoE protein is present (Riddell et al., 2008). Almost as soon as it was appreciated that the presence of the apoE4 allele was robustly associated with an increased risk of developing most forms of AD (Corder et al., 1993), two apparently unrelated threads of research on apoE function developed. One was based on connecting apoE, through its lipid-binding domain, to the formation of the A β and hyperphosphorylated τ , the histologically discernible proteins historically associated with AD (Strittmatter et al., 1993, 1994). The other thread, not lipid-related, focusing on innate immunity and inflammatory mediators rather than lipids, sought

to explain why the link between apoE4 and disease risk was far wider than AD, encompassing traumatic brain injury and stroke, and bacterial infections (Roselaar and Daugherty, 1998; de Bont et al., 1999), which have all been argued to be inflammatory conditions since the early 1990s. Indeed, the apoE4 connection with disease susceptibility goes as far as HIV dementia (Corder et al., 1998) and cerebral malaria (Aucan et al., 2004).

This second line of enquiry led to seminal outcomes such as suppression of glial cell secretion of TNF by apoE (Laskowitz et al., 1997) and inhibition of glial cell activation and the endogenous CNS inflammatory response (Lynch et al., 2001) and the general type 1 inflammatory response (Ali et al., 2005), which is mediated by cytokines such as TNF and IL-1 β . A comprehensive review of these concepts appeared 3 years ago (Vitek et al., 2009). This approach has led to the attainment of a clinically useful anti-inflammatory milieu in many mouse models of inflammatory disease by subcutaneous injection of segments of the apoE molecule (apoE mimetics) that are small enough to enter the brain. This duplicates the anti-inflammatory action of complete apoE (Laskowitz et al., 2001). Examples include traumatic brain injury (Lynch et al., 2005; Laskowitz et al., 2007; Hoane et al., 2009; Kaufman et al., 2010), stroke (Tukhovskaya et al., 2009), and AD (Vitek et al., 2012).

Cramer et al. (2012) describe removal of A β plaque and correction of functional deficits in a strain of mice prone to AD-like changes after oral administration of bexarotene, an anti-tumor drug in clinical use. This agent is small enough to enter the brain, where it increases endogenous apoE levels through its activity as a retinoid X receptor agonist. In a functional sense, bexarotene therefore promises to be the equivalent of the apoE mimetics. Surprisingly, A β plaque removal was the only mechanism considered by these authors, despite the doubt cast on the utility of this endpoint by the AD patient trial of AN1792 (A β 42; Elan Pharmaceuticals, South San Francisco, CA) several years ago (Holmes et al., 2008). It is useful to recall, when interpreting

TABLE 1

A reference guide for the treatment concepts embodied in this review, and their consequences, either intended by the authors or predictable from the literature

Treatment Concepts	Predictable Consequences in the Brain	Predictable Downstream Consequences in the Brain	Reference
apoE mimetics	↓ TNF	↓ Insulin resistance	Laskowitz et al., 2001
Thalidomide derivatives	↓ TNF	↓ Insulin resistance	Greig et al., 2004a
Anti-TNF biologicals	↓ TNF	↓ Insulin resistance	Tobinick et al., 2006
Minoocycline	↓ TNF	↓ Insulin resistance	Seabrook et al., 2006
Leuprolide	↓ TNF	↓ Insulin resistance	Clark and Atwood, 2011
Curcumin derivatives	↓ TNF	↓ Insulin resistance	Tsai et al., 2011
Erythropoietin	↓ TNF	↓ Insulin resistance	Nairz et al., 2011a
Bexarotene	↓ TNF	↓ Insulin resistance	Cramer et al. 2012
GLP-1 mimetics	↓ Insulin resistance	↓ GSK3 activation	Perry et al., 2003
Intranasal insulin	↓ Insulin resistance	↓ GSK3 activation	Benedict et al., 2004
Leptin	↓ Insulin resistance	↓ GSK3 activation	Koch et al., 2010
DPP-4 inhibitors	↓ Insulin resistance	↓ GSK3 activation	D'Amico et al., 2010
GSK-3 antagonists	↓ GSK3 activation	↓ Harmful enzyme phosphorylation	Onishi et al., 2011

↓, reduction.

this bexarotene data, that anti-TNF treatment produces a very similar outcome in the same mouse model (Shi et al., 2011), and an apoE mimetic has since done so in a related mouse strain (Vitek et al., 2012). Literature exists on the side effects of bexarotene, but whether these arise from high apoE or other consequences of retinoid X receptor activation has yet to be determined.

XII. Conclusions

It seems not yet to have been taken into account in AD research that TNF and related inflammatory cytokines induce insulin resistance or that SZT also induces TNF. The introduction of these concepts into this field consolidates numerous non-A β models of AD. Accordingly, numerous proposed treatments for AD, presently undertaken with different rationales, seem to be functionally linked by events that lower TNF levels (and thus insulin resistance), lower insulin resistance directly, or deal with its consequences. These presently independent sets of arguments for therapy reinforce the logic of chronic cerebral insulin resistance and, therefore, the degree to which GSK-3 activation, and thus mitochondrial dysfunction, is central to understanding this disease. We have reasoned that these superficially unrelated approaches to treatment are all aimed at chronic inflammation and its consequences. Thus, they are, in a sense, one tool, which invites collaborative searches for therapeutic synergy.

When considering how rapidly the therapies discussed in this review might have the opportunity to demonstrate whether they can help patients, we note that anti-TNF biological agents, minocycline, and GLP-1 mimetics already have a history of clinical use for other conditions, the first two for much longer, and on a much larger scale, than the third. Intranasal insulin has been used in human trials, produced no side effects, and seems innately harmless at such doses. Leptin, like insulin an endogenous molecule, has been used long-term in a small number of patients without apparent harm, whereas EPO variants still require basic toxicity and efficacy studies. ApoE mimetics and GSK-3 inhibitors warrant extending beyond rodent models.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Clark, Atwood, Bowen, Paz-Filho, and Vissel.

References

- Abbas A, Imrie H, Viswambharan H, Sukumar P, Rajwani A, Cubbon RM, Gage M, Smith J, Galloway S, Yuldesheva N, et al. (2011) The insulin-like growth factor-1 receptor is a negative regulator of nitric oxide bioavailability and insulin sensitivity in the endothelium. *Diabetes* **60**:2169–2178.
- Abbatecola AM, Paolisso G, Lamponi M, Bandinelli S, Lauretani F, Launer L, and Ferrucci L (2004) Insulin resistance and executive dysfunction in older persons. *J Am Geriatr Soc* **52**:1713–1718.
- Abdipranoto-Cowley A, Park JS, Croucher D, Daniel J, Henshall S, Galbraith S, Mervin K, and Vissel B (2009) Activin A is essential for neurogenesis following neurodegeneration. *Stem Cells* **27**:1330–1346.
- Adamcio B, Sargin D, Stradomska A, Medrihan L, Gertler C, Theis F, Zhang M, Müller M, Hassouna I, Hannke K, et al. (2008) Erythropoietin enhances hippocampal long-term potentiation and memory. *BMC Biol* **6**:37.
- Adamo M, Raizada MK, and LeRoith D (1989) Insulin and insulin-like growth factor receptors in the nervous system. *Mol Neurobiol* **3**:71–100.
- Adams S, Brown H, and Turner G (2002) Breaking down the blood-brain barrier: signaling a path to cerebral malaria? *Trends Parasitol* **18**:360–366.
- Aggarwal BB, Kohr WJ, Hass PE, Moffat B, Spencer SA, Henzel WJ, Bringman TS, Nedwin GE, Goeddel DV, and Harkins RN (1985) Human tumor necrosis factor. Production, purification, and characterization. *J Biol Chem* **260**:2345–2354.
- Ahrén B (2009) Clinical results of treating type 2 diabetic patients with sitagliptin, vildagliptin or saxagliptin—diabetes control and potential adverse events. *Best Pract Res Clin Endocrinol Metab* **23**:487–498.
- Ahrén B (2011a) The future of incretin-based therapy: novel avenues—novel targets. *Diabetes Obes Metab* **13** (Suppl 1):158–166.
- Ahrén B (2011b) GLP-1 for type 2 diabetes. *Exp Cell Res* **317**:1239–1245.
- Ahrén B and Foley JE (2008) The islet enhancer vildagliptin: mechanisms of improved glucose metabolism. *Int J Clin Pract Suppl* (159):8–14.
- Albrow J, Kayal RA, Siqueira M, Siqueria M, McKenzie E, Krothapalli N, McLean J, Conn J, Nikolajczyk B, Einhorn TA, et al. (2009) High levels of tumor necrosis factor- α contribute to accelerated loss of cartilage in diabetic fracture healing. *Am J Pathol* **175**:1574–1585.
- Alexander JJ, Jacob A, Cunningham P, Hensley L, and Quigg RJ (2008) TNF is a key mediator of septic encephalopathy acting through its receptor, TNF receptor-1. *Neurochem Int* **52**:447–456.
- Ali K, Middleton M, Puré E, and Rader DJ (2005) Apolipoprotein E suppresses the type I inflammatory response in vivo. *Circ Res* **97**:922–927.
- Alkam T, Nitta A, Mizoguchi H, Saito K, Seshima M, Itoh A, Yamada K, and Nabeshima T (2008) Restraining tumor necrosis factor- α by thalidomide prevents the amyloid beta-induced impairment of recognition memory in mice. *Behav Brain Res* **189**:100–106.
- Anderson EJ, Lustig ME, Boyle KE, Woodlief TL, Kane DA, Lin CT, Price JW, 3rd, Kang L, Rabinovitch PS, et al. (2009) Mitochondrial H₂O₂ emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans. *J Clin Invest* **119**:573–581.
- Araújo EP, De Souza CT, Ueno M, Cintra DE, Bertolo MB, Carvalheira JB, Saad MJ, and Velloso LA (2007) Infliximab restores glucose homeostasis in an animal model of diet-induced obesity and diabetes. *Endocrinology* **148**:5991–5997.
- Arruda AP, Milanski M, Coope A, Torsoni AS, Ropelle E, Carvalho DP, Carvalheira JB, and Velloso LA (2011) Low-grade hypothalamic inflammation leads to defective thermogenesis, insulin resistance, and impaired insulin secretion. *Endocrinology* **152**:1314–1326.
- Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, and Bennett DA (2004) Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Arch Neurol* **61**:661–666.
- Asthana S, Baker LD, Craft S, Stanczyk FZ, Veith RC, Raskind MA, and Plymate SR (2001) High-dose estradiol improves cognition for women with AD: results of a randomized study. *Neurology* **57**:605–612.
- Atwood CS (2010) Amyloid-beta aggregation as a protective acute-phase response to injury/neurodegeneration: a barrier function for amyloid-beta deposits, in *Functional Amyloid Aggregation* (Rigacci S and Bucciantini M eds) pp 115–134, Research Signpost, Kerala, India.
- Atwood CS, Bishop GM, Perry G, and Smith MA (2002) Amyloid-beta: a vascular sealant that protects against hemorrhage? *J Neurosci Res* **70**:356.
- Aucan C, Walley AJ, and Hill AV (2004) Common apolipoprotein E polymorphisms and risk of clinical malaria in the Gambia. *Journal of Medical Genetics* **41**:21–24.
- Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, and Craft S (2011) Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. *Arch Neurol* **68**:51–57.
- Balaraman Y, Limaye AR, Levey AI, and Srinivasan S (2006) Glycogen synthase kinase 3 β and Alzheimer's disease: pathophysiological and therapeutic significance. *Cell Mol Life Sci* **63**:1226–1235.
- Ballard C and Walker M (1999) Neuropsychiatric aspects of Alzheimer's disease. *Curr Psychiatry Rep* **1**:49–60.
- Bate CA, Taverne J, and Playfair JH (1989) Soluble malarial antigens are toxic and induce the production of tumour necrosis factor in vivo. *Immunology* **66**:600–605.
- Beier K, Völk A, and Fahimi HD (1997) TNF- α downregulates the peroxisome proliferator activated receptor- α and the mRNAs encoding peroxisomal proteins in rat liver. *FEBS Lett* **412**:385–387.
- Belarbi K, Arellano C, Ferguson R, Jopson T, and Rosi S (2012a) Chronic neuroinflammation impacts the recruitment of adult-born neurons into behaviorally relevant hippocampal networks. *Brain Behav Immun* **26**:18–23.
- Belarbi K, Jopson T, Tweedie D, Arellano C, Luo W, Greig NH, and Rosi S (2012b) TNF- α protein synthesis inhibitor restores neuronal function and reverses cognitive deficits induced by chronic neuroinflammation. *J Neuroinflammation* **9**:23.
- Benedict C, Brooks SJ, Kullberg J, Burgos J, Kempton MJ, Nordenskjöld R, Nylander R, Kilander L, Craft S, Larsson EM, et al. (2012) Impaired insulin sensitivity as indexed by the HOMA score is associated with deficits in verbal fluency and temporal lobe gray matter volume in elderly men and women. *Diabetes Care* **35**:488–494.
- Benedict C, Hallschmid M, Hatke A, Schultes B, Fehm HL, Born J, and Kern W (2004) Intranasal insulin improves memory in humans. *Psychoneuroendocrinology* **29**:1326–1334.
- Bernardino L, Agasse F, Silva B, Ferreira R, Grade S, and Malva JO (2008) Tumor necrosis factor- α modulates survival, proliferation, and neuronal differentiation in neonatal subventricular zone cell cultures. *Stem Cells* **26**:2361–2371.
- Berry A, Tomidokoro Y, Ghiso J, and Thornton J (2008) Human chorionic gonadotropin (a luteinizing hormone homologue) decreases spatial memory and increases brain amyloid-beta levels in female rats. *Horm Behav* **54**:143–152.
- Beutler B, Greenwald D, Hulmes JD, Chang M, Pan YC, Mathison J, Ulevitch R, and Cerami A (1985) Identity of tumour necrosis factor and the macrophage-secreted factor cachectin. *Nature* **316**:552–554.
- Beutler B and Poltorak A (2001) Sepsis and evolution of the innate immune response. *Crit Care Med* **29**:S2–S6.

- Blass JP and Gibson GE (1991) The role of oxidative abnormalities in the pathophysiology of Alzheimer's disease. *Rev Neurol* **147**:513–525.
- Blondel O and Portha B (1989) Early appearance of *in vivo* insulin resistance in adult streptozotocin-injected rats. *Diabetes Metab* **15**:382–387.
- Bluthé RM, Pawlowski M, Suarez S, Parnet P, Pittman Q, Kelley KW, and Dantzer R (1994) Synergy between tumor necrosis factor alpha and interleukin-1 in the induction of sickness behavior in mice. *Psychoneuroendocrinology* **19**:197–207.
- Boehm J, Fischer K, and Bohnert M (2010) Putative role of TNF-alpha, interleukin-8 and ICAM-1 as indicators of an early inflammatory reaction after burn: a morphological and immunohistochemical study of lung tissue of fire victims. *J Clin Pathol* **63**:967–971.
- Bohac D, Burke W, Cotter R, Zheng J and Potter J (2002) A 24-week randomized, double-blind, placebo-controlled study of the efficacy and tolerability of TNFR: Fc (etanercept) in the treatment of dementia of the Alzheimer type (Abstract 315). *Neurobiol Aging* **23** (Suppl 1):S1–S606.
- Boivin MJ, Bangirana P, Byarugaba J, Opoka RO, Idro R, Jurek AM, and John CC (2007) Cognitive impairment after cerebral malaria in children: a prospective study. *Pediatrics* **119**:e360–e366.
- Bomfim TR, Fornhy-Germano L, Sathler LB, Brito-Moreira J, Houzel JC, Decker H, Silverman MA, Kazi H, Melo HM, McClean PL, et al. (2012) An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease-associated Abeta oligomers. *J Clin Invest* **122**:1339–1353.
- Borger E, Aitken L, Muirhead KE, Allen ZE, Ainge JA, Conway SJ, and Gunn-Moore FJ (2011) Mitochondrial beta-amyloid in Alzheimer's disease. *Biochem Soc Trans* **39**:868–873.
- Borgs L, Beukelaers P, Vandenbosch R, Nguyen L, Moonen G, Maquet P, Albrecht U, Belachew S, and Malgrange B (2009) Period 2 regulates neural stem/progenitor cell proliferation in the adult hippocampus. *BMC Neurosci* **10**:30.
- Born J, Lange T, Kern W, McGregor GP, Bickel U, and Fehm HL (2002) Sniffing neuropeptides: a transnasal approach to the human brain. *Nat Neurosci* **5**:514–516.
- Bour ES, Ward LK, Cormman GA, and Isom HC (1996) Tumor necrosis factor-alpha-induced apoptosis in hepatocytes in long-term culture. *Am J Pathol* **148**:485–495.
- Bowen RL and Atwood CS (2004) Living and dying for sex. A theory of aging based on the modulation of cell cycle signaling by reproductive hormones. *Gerontology* **50**:265–290.
- Bowen RL, Verdile G, Liu T, Parlow AF, Perry G, Smith MA, Martins RN, and Atwood CS (2004) Luteinizing hormone, a reproductive regulator that modulates the processing of amyloid-beta precursor protein and amyloid-beta deposition. *J Biol Chem* **279**:20539–20545.
- Boydjjeva NI and Sarkar DK (2010) Role of microglia in ethanol's apoptotic action on hypothalamic neuronal cells in primary cultures. *Alcohol Clin Exp Res* **34**:1835–1842.
- Brennan FM, Chantry D, Jackson A, Maini R, and Feldmann M (1989) Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. *Lancet* **2**:244–247.
- Brugg B, Dubreuil YL, Huber G, Wollman EE, Delhaye-Bouchaud N, and Mariani J (1995) Inflammatory processes induce beta-amyloid precursor protein changes in mouse brain. *Proc Natl Acad Sci USA* **92**:3032–3035.
- Bryan KJ, Mudd JC, Richardson SL, Chang J, Lee HG, Zhu X, Smith MA, and Casadesus G (2010) Down-regulation of serum gonadotropins is as effective as estrogen replacement at improving menopause-associated cognitive deficits. *J Neurochem* **112**:870–881.
- Bryant NJ, Govers R, and James DE (2002) Regulated transport of the glucose transporter GLUT4. *Nat Rev Mol Cell Biol* **3**:267–277.
- Buchhave P, Zetterberg H, Blennow K, Minthon L, Janciauskiene S, and Hansson O (2010) Soluble TNF receptors are associated with Abeta metabolism and conversion to dementia in subjects with mild cognitive impairment. *Neurobiol Aging* **31**:1877–1884.
- Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, Zychma M, Blonde L, and LEAD-6 Study Group (2009) Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* **374**:39–47.
- Buxbaum JD, Liu KN, Luo Y, Slack JL, Stocking KL, Peschon JJ, Johnson RS, Castner BJ, Cerretti DP, and Black RA (1998) Evidence that tumor necrosis factor alpha converting enzyme is involved in regulated alpha-secretase cleavage of the Alzheimer amyloid protein precursor. *J Biol Chem* **273**:27765–27767.
- Cabou C, Campistron G, Marsollier N, Leloup C, Cruciani-Guglielmacci C, Pénicaud L, Drucker DJ, Magnan C, and Burcelin R (2008) Brain glucagon-like peptide-1 regulates arterial blood flow, heart rate, and insulin sensitivity. *Diabetes* **57**:2577–2587.
- Cai Z, Zhao Y, Yao S, and Bin Zhao B (2011) Increases in beta-amyloid protein in the hippocampus caused by diabetic metabolic disorder are blocked by minocycline through inhibition of NF-kappaB pathway activation. *Pharmacol Rep* **63**:381–391.
- Calleja AI, García-Bermejo P, Cortijo E, Bustamante R, Rojo Martínez E, González Sarmiento E, Fernández-Herranz R, and Arenillas JF (2011) Insulin resistance is associated with a poor response to intravenous thrombolysis in acute ischemic stroke. *Diabetes Care* **34**:2413–2417.
- Campbell JH, Burdo TH, Attissier P, Bombardier JP, Westmoreland SV, Soulas C, González RG, Ratai EM, and Williams KC (2011) Minocycline inhibition of monocyte activation correlates with neuronal protection in SIV neuroAIDS. *PLoS One* **6**:e18688.
- Carraway MS, Suliman HB, Jones WS, Chen CW, Babiker A, and Piantadosi CA (2010) Erythropoietin activates mitochondrial biogenesis and couples red cell mass to mitochondrial mass in the heart. *Circ Res* **106**:1722–1730.
- Carroll JC, Rosario ER, Chang L, Stanczyk FZ, Oddo S, LaFerla FM, and Pike CJ (2007) Progesterone and estrogen regulate Alzheimer-like neuropathology in female 3xTg-AD mice. *J Neurosci* **27**:13357–13365.
- Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, and Williamson B (1975) An endotoxin-induced serum factor that causes necrosis of tumors. *Proc Natl Acad Sci USA* **72**:3666–3670.
- Carter JA, Mung'ala-Odera V, Neville BG, Murira G, Mturi N, Musumba C, and Newton CR (2005) Persistent neurocognitive impairments associated with severe falciparum malaria in Kenyan children. *J Neurol Neurosurg Psychiatry* **76**:476–481.
- Casadesus G, Milliken EL, Webber KM, Bowen RL, Lei Z, Rao CV, Perry G, Keri RA, and Smith MA (2007) Increases in luteinizing hormone are associated with declines in cognitive performance. *Mol Cell Endocrinol* **269**:107–111.
- Casadesus G, Webber KM, Atwood CS, Pappolla MA, Perry G, Bowen RL, and Smith MA (2006) Luteinizing hormone modulates cognition and amyloid-beta deposition in Alzheimer APP transgenic mice. *Biochim Biophys Acta* **1762**:447–452.
- Casals-Pascual C, Idro R, Gicheru N, Gwer S, Kitsao B, Gitau E, Mwakesi R, Roberts DJ, and Newton CR (2008) High levels of erythropoietin are associated with protection against neurological sequelae in African children with cerebral malaria. *Proc Natl Acad Sci USA* **105**:2634–2639.
- Casals-Pascual C, Idro R, Picot S, Roberts DJ, and Newton CR (2009) Can erythropoietin be used to prevent brain damage in cerebral malaria? *Trends Parasitol* **25**:30–36.
- Castellani R, Hirai K, Aliev G, Drew KL, Nunomura A, Takeda A, Cash AD, Obrenovich ME, Perry G, and Smith MA (2002) Role of mitochondrial dysfunction in Alzheimer's disease. *J Neurosci Res* **70**:357–360.
- Cavadini G, Petrzilka S, Kohler P, Jud C, Tobler I, Birchler T, and Fontana A (2007) TNF-alpha suppresses the expression of clock genes by interfering with E-box-mediated transcription. *Proc Natl Acad Sci USA* **104**:12843–12848.
- Célerier P, Litoux P, and Dréno B (1996) *In vitro* modulation of epidermal inflammatory cytokines (IL-1 alpha, IL-6, TNF alpha) by minocycline. *Arch Dermatol Res* **288**:411–414.
- Chan MM (1995) Inhibition of tumor necrosis factor by curcumin, a phytochemical. *Biochem Pharmacol* **49**:1551–1556.
- Charles P, Elliott MJ, Davis D, Potter A, Kalden JR, Antoni C, Breedveld FC, Smolen JS, Eberl G, deWoody K, et al. (1999) Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF-alpha therapy in rheumatoid arthritis. *J Immunol* **163**:1521–1528.
- Chateauxvieux S, Grigorakaki C, Morceau F, Dicato M, and Diederich M (2011) Erythropoietin, erythropoiesis and beyond. *Biochem Pharmacol* **82**:1291–1303.
- Chaudry IH, Sayeed MM, and Baue AE (1974) Insulin resistance in experimental shock. *Arch Surg* **109**:412–415.
- Chawla A, Nguyen KD, and Goh YP (2011) Macrophage-mediated inflammation in metabolic disease. *Nat Rev Immunol* **11**:738–749.
- Chen KB, Uchida K, Nakajima H, Yayama T, Hirai T, Watanabe S, Guerrero AR, Kobayashi S, Ma WY, Liu SY, et al. (2011) Tumor necrosis factor-alpha antagonist reduces apoptosis of neurons and oligodendroglia in rat spinal cord injury. *Spine* **36**:1350–1358.
- Chen XH, Zhao YP, Xue M, Ji CB, Gao CL, Zhu JG, Qin DN, Kou CZ, Qin XH, Tong ML, et al. (2010) TNF-alpha induces mitochondrial dysfunction in 3T3-L1 adipocytes. *Mol Cell Endocrinol* **328**:63–69.
- Cheng H, Woodgett J, Maamari M, and Force T (2011) Targeting GSK-3 family members in the heart: a very sharp double-edged sword. *J Mol Cell Cardiol* **51**:607–613.
- Cheng HH, Ma CY, Chou TW, Chen YY, and Lai MH (2010) Gamma-oryzanol ameliorates insulin resistance and hyperlipidemia in rats with streptozotocin/nicotinamide-induced type 2 diabetes. *Int J Vitam Nutr Res* **80**:45–53.
- Chio CC, Lin JW, Chang MW, Wang CC, Kuo JR, Yang CZ, and Chang CP (2010) Therapeutic evaluation of etanercept in a model of traumatic brain injury. *J Neurochem* **115**:921–929.
- Chiu SS, Lui E, Majeed M, Vishwanatha JK, Ranjan AP, Maitra A, Pramanik D, Smith JA, and Helson L (2011) Differential distribution of intravenous curcumin formulations in the rat brain. *Anticancer Res* **31**:907–911.
- Choi Y, Kim HS, Shin KY, Kim EM, Kim M, Kim HS, Park CH, Jeong YH, Yoo J, Lee JP, et al. (2007) Minocycline attenuates neuronal cell death and improves cognitive impairment in Alzheimer's disease models. *Neuropsychopharmacology* **32**:2393–2404.
- Chowdhury SK, Zherebitskaya E, Smith DR, Akude E, Chattopadhyay S, Jolivald CG, Calcult NA, and Fernyhough P (2010) Mitochondrial respiratory chain dysfunction in dorsal root ganglia of streptozotocin-induced diabetic rats and its correction by insulin treatment. *Diabetes* **59**:1082–1091.
- Church RF, Schaub RE, and Weiss MJ (1971) Synthesis of 7-dimethylamino-6-demethyl-6-deoxytetracycline (minocycline) via 9-nitro-6-demethyl-6-deoxytetracycline. *J Org Chem* **36**:723–725.
- Clark IA, Alleva LM, and Vissel B (2010) The roles of TNF in brain dysfunction and disease. *Pharmacol Ther* **128**:519–548.
- Clark IA, Alleva LM, and Vissel B (2011) TNF and leptin tell essentially the same story in Alzheimer's disease. *J Alzheimers Dis* **26**:201–205.
- Clark IA and Atwood CS (2011) Is TNF a link between aging-related reproductive endocrine dyscrasia and Alzheimer's disease? *J Alzheimers Dis* **27**:691–699.
- Clark IA, Budd AC, and Alleva LM (2008) Sickness behaviour pushed too far—the basis of the syndrome seen in severe protozoal, bacterial and viral diseases and post-trauma. *Malar J* **7**:208.
- Clark IA and Chaudhri G (1988) Tumour necrosis factor may contribute to the anaemia of malaria by causing dyserythropoiesis and erythrophagocytosis. *Br J Haematol* **70**:99–103.
- Clark IA, Virelizier JL, Carswell EA, and Wood PR (1981) Possible importance of macrophage-derived mediators in acute malaria. *Infect Immun* **32**:1058–1066.
- Cole GM, Teter B, and Frautschy SA (2007) Neuroprotective effects of curcumin. *Adv Exp Med Biol* **595**:197–212.
- Coleman DL, Leiter EH, and Schwizer RW (1982) Therapeutic effects of dehydroepiandrosterone (DHEA) in diabetic mice. *Diabetes* **31**:830–833.
- Corder EH, Robertson K, Lannfelt L, Bogdanovic N, Eggertsen G, Wilkins J, and Hall C (1998) HIV-infected subjects with the E4 allele for APOE have excess dementia and peripheral neuropathy. *Nat Med* **4**:1182–1184.
- Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, and Pericak-Vance MA (1993) Gene dose of apolipoprotein E

- type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261**:921–923.
- Correia SC, Santos RX, Perry G, Zhu X, Moreira PI, and Smith MA (2011) Insulin-resistant brain state: the culprit in sporadic Alzheimer's disease? *Ageing Res Rev* **10**:264–273.
- Craft S, Asthana S, Newcomer JW, Wilkinson CW, Matos IT, Baker LD, Cherrier M, Lofgren C, Latendresse S, Petrova A, et al. (1999) Enhancement of memory in Alzheimer disease with insulin and somatostatin, but not glucose. *Arch Gen Psychiatry* **56**:1135–1140.
- Craft S, Newcomer J, Kanne S, Dagogo-Jack S, Cryer P, Sheline Y, Luby J, Dagogo-Jack A, and Alderson A (1996) Memory improvement following induced hyperinsulinemia in Alzheimer's disease. *Neurobiol Aging* **17**:123–130.
- Cramer PE, Cirrito JR, Wesson DW, Lee CY, Karlo JC, Zinn AE, Casali BT, Restivo JL, Goebel WD, James MJ, et al. (2012) ApoE-directed therapeutics rapidly clear beta-amyloid and reverse deficits in AD mouse models. *Science* **335**:1503–1506.
- Cross DA, Alessi DR, Cohen P, Andjelkovich M, and Hemmings BA (1995) Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. *Nature* **378**:785–789.
- Cubbon RM, Kahn MB, and Wheatcroft SB (2009) Effects of insulin resistance on endothelial progenitor cells and vascular repair. *Clin Sci (Lond)* **117**:173–190.
- D'Amico M, Di Filippo C, Marfella R, Abbatecola AM, Ferraraccio F, Rossi F, and Paolisso G (2010) Long-term inhibition of dipeptidyl peptidase-4 in Alzheimer's prone mice. *Exp Gerontol* **45**:202–207.
- Dantzer R and Kelley KW (2007) Twenty years of research on cytokine-induced sickness behavior. *Brain Behav Immun* **21**:153–160.
- Darzynkiewicz Z, Williamson B, Carswell EA, and Old LJ (1984) Cell cycle-specific effects of tumor necrosis factor. *Cancer Res* **44**:83–90.
- Das S, Dutta K, Kumawat KL, Ghoshal A, Adhya D, and Basu (2011) A Abrogated inflammatory response promotes neurogenesis in a murine model of Japanese encephalitis. *PLoS One* **6**:e17225.
- Davis TM, Brown AE, and Smith CD (1993) Metabolic disturbances in *Plasmodium coatneyi*-infected rhesus monkeys. *Int J Parasitol* **23**:557–563.
- de Bont N, Netea MG, Demacker PN, Verschueren I, Kullberg BJ, van Dijk KW, van der Meer JW, and Stalenhoef AF (1999) Apolipoprotein E knock-out mice are highly susceptible to endotoxemia and *Klebsiella pneumoniae* infection. *J Lipid Res* **40**:680–685.
- de Castro J, Sevillano J, Marciniak J, Rodriguez R, González-Martín C, Viana M, Eun-suk OH, de Mouzon SH, Herrera E, and Ramos MP (2011) Implication of low level inflammation in the insulin resistance of adipose tissue at late pregnancy. *Endocrinology* **152**:4094–4105.
- de la Monte SM, Tong M, Bowling N, and Moskal P (2011) si-RNA inhibition of brain insulin or insulin-like growth factor receptors causes developmental cerebellar abnormalities: relevance to fetal alcohol spectrum disorder. *Mol Brain* **4**:13.
- de la Monte SM and Wands JR (2008) Alzheimer's disease is type 3 diabetes-evidence reviewed. *J Diabetes Sci Technol* **2**:1101–1113.
- de la Monte SM and Wands JR (2010) Role of central nervous system insulin resistance in fetal alcohol spectrum disorders. *J Popul Ther Clin Pharmacol* **17**:e390–404.
- de la Monte SM, Xu XJ, and Wands JR (2005) Ethanol inhibits insulin expression and actions in the developing brain. *Cell Mol Life Sci* **62**:1131–1145.
- Desouza CV, Hamel FG, Bidasee K, and O'Connell K (2011) Role of inflammation and insulin resistance in endothelial progenitor cell dysfunction. *Diabetes* **60**:1286–1294.
- Devaraj S, Tobias P, and Jialal I (2011) Knockout of toll-like receptor-4 attenuates the pro-inflammatory state of diabetes. *Cytokine* **55**:441–445.
- Diehl AM and Rai R (1996) Review: regulation of liver regeneration by pro-inflammatory cytokines. *J Gastroenterol Hepatol* **11**:466–470.
- Doble BW and Woodgett JR (2003) GSK-3: tricks of the trade for a multi-tasking kinase. *J Cell Sci* **116**:1175–1186.
- Dugo L, Collin M, Allen DA, Murch O, Foster SJ, Yaqoob MM, and Thiemermann C (2006) Insulin reduces the multiple organ injury and dysfunction caused by coadministration of lipopolysaccharide and peptidoglycan independently of blood glucose: role of glycogen synthase kinase-3beta inhibition. *Crit Care Med* **34**:1489–1496.
- During MJ, Cao L, Zuzga DS, Francis JS, Fitzsimons HL, Jiao X, Bland RJ, Klugmann M, Banks WA, Drucker DJ, et al. (2003) Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. *Nat Med* **9**:1173–1179.
- Eltahir EM, El Ghazali G, A-Elgadir TM, A-Elbasit IE, Elbasher MI, and Giha HA (2010a) Raised plasma insulin level and homeostasis model assessment (HOMA) score in cerebral malaria: evidence for insulin resistance and marker of virulence. *Acta Biochim Pol* **57**:513–520.
- Eltahir EM, El Ghazali G, A-Elgadir TM, A-Elbasit IE, Elbasher MI, and Giha HA (2010b) Raised plasma insulin level and homeostasis model assessment (HOMA) score in cerebral malaria: evidence for insulin resistance and marker of virulence. *Acta Biochim Pol* **57**:513–520.
- Embi N, Rylatt DB, and Cohen P (1980) Glycogen synthase kinase-3 from rabbit skeletal muscle. Separation from cyclic-AMP-dependent protein kinase and phosphorylase kinase. *Eur J Biochem* **107**:519–527.
- Engel T, Hernández F, Avila J, and Lucas JJ (2006) Full reversal of Alzheimer's disease-like phenotype in a mouse model with conditional overexpression of glycogen synthase kinase-3. *J Neurosci* **26**:5083–5090.
- Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, van Swieten JC, Stijnen T, Hofman A, Wittman JC, and Breteler MM (2004) Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. *Arch Neurol* **61**:668–672.
- Extance A (2010) Alzheimer's failure raises questions about disease-modifying strategies. *Nat Rev Drug Discov* **9**:749–751.
- Familian A, Boshuizen RS, Eikelenboom P, and Veerhuis R (2006) Inhibitory effect of minocycline on amyloid beta fibril formation and human microglial activation. *Glia* **53**:233–240.
- Fan R, Xu F, Previti ML, Davis J, Grande AM, Robinson JK, and Van Nostrand WE (2007) Minocycline reduces microglial activation and improves behavioral deficits in a transgenic model of cerebral microvascular amyloid. *J Neurosci* **27**:3057–3063.
- Fassbender K, Walter S, Kühl S, Landmann R, Ishii K, Bertsch T, Stalder AK, Muehlhauser F, Liu Y, Ulmer AJ, et al. (2004) The LPS receptor (CD14) links innate immunity with Alzheimer's disease. *FASEB J* **18**:203–205.
- Feinstein R, Kanety H, Papa MZ, Lunenfeld B, and Karasik A (1993) Tumor necrosis factor-alpha suppresses insulin-induced tyrosine phosphorylation of insulin receptor and its substrates. *J Biol Chem* **268**:26055–26058.
- Ferdaoussi M, Abdelli S, Yang JY, Cornu M, Niederhauser G, Favre D, Widmann C, Regazzi R, Thorens B, Waeber G, et al. (2008) Exendin-4 protects beta-cells from interleukin-1 beta-induced apoptosis by interfering with the c-Jun NH2-terminal kinase pathway. *Diabetes* **57**:1205–1215.
- Ferraz-Amaro I, Arce-Franco M, Muñoz J, López-Fernández J, Hernández-Hernández V, Franco A, Quevedo J, Martínez-Martín J, and Díaz-González F (2011) Systemic blockade of TNF-alpha does not improve insulin resistance in humans. *Horm Metab Res* **43**:801–808.
- Ferreira RA, Vieira CS, Rosa-E-Silva JC, Rosa-e-Silva AC, Nogueira AA, and Ferriani RA (2010) Effects of the levonorgestrel-releasing intrauterine system on cardiovascular risk markers in patients with endometriosis: a comparative study with the GnRH analogue. *Contraception* **81**:117–122.
- Ficiocioglu C, Kumbak B, Akcin O, Attar R, Yildirim G, and Yesildaglar N (2010) Comparison of follicular fluid and serum cytokine concentrations in women undergoing assisted reproductive treatment with GnRH agonist long and antagonist protocols. *Gynecol Endocrinol* **26**:181–186.
- Fink M (1997) Cytopathic hypoxia in sepsis. *Acta Anaesthesiol Scand Suppl* **110**:87–95.
- Fink MP (2000) Cytopathic hypoxia. A concept to explain organ dysfunction in sepsis. *Minerva Anesthesiol* **66**:337–342.
- Fink MP (2001) Cytopathic hypoxia. Mitochondrial dysfunction as mechanism contributing to organ dysfunction in sepsis. *Crit Care Clin* **17**:219–237.
- Forsythe ME, Love DC, Lazarus BD, Kim EJ, Prinz WA, Ashwell G, Krause MW, and Hanover JA (2006) Caenorhabditis elegans ortholog of a diabetes susceptibility locus: oga-1 (O-GlcNAcase) knockout impacts O-GlcNAc cycling, metabolism, and dauer. *Proc Natl Acad Sci USA* **103**:11952–11957.
- Fraker DL, Merino MJ, and Norton JA (1989) Reversal of the toxic effects of cachectin by concurrent insulin administration. *Am J Physiol* **256**:E725–E731.
- Frankel SK, Cosgrove GP, Cha SI, Cool CD, Wynes MW, Edelman BL, Brown KK, and Riches DW (2006) TNF-alpha sensitizes normal and fibrotic human lung fibroblasts to Fas-induced apoptosis. *Am J Respir Cell Mol Biol* **34**:293–304.
- Frayn KN (1975) Effects of burn injury on insulin secretion and on sensitivity to insulin in the rat in vivo. *Eur J Clin Invest* **5**:331–337.
- Frye CA, Duffy CK, and Wolf AA (2007) Estrogens and progestins enhance spatial learning of intact and ovariectomized rats in the object placement task. *Neurobiol Learn Mem* **88**:208–216.
- Fujikawa T, Chuang JC, Sakata I, Ramadori G, and Coppari R (2010) Leptin therapy improves insulin-deficient type 1 diabetes by CNS-dependent mechanisms in mice. *Proc Natl Acad Sci USA* **107**:17391–17396.
- Games D, Buttini M, Kobayashi D, Schenk D, and Seubert P (2006) Mice as models: transgenic approaches and Alzheimer's disease. *J Alzheimers Dis* **9**:133–149.
- Garrabou G, Morén C, López S, Tobías E, Cardellach F, Miró O, and Casademont J (2012) The effects of sepsis on mitochondria. *J Infect Dis* **205**:392–400.
- Garwood CJ, Cooper JD, Hanger DP, and Noble W (2010) Anti-inflammatory impact of minocycline in a mouse model of tauopathy. *Front Psychiatry* **1**:136.
- Garwood CJ, Pooler AM, Atherton J, Hanger DP, and Noble W (2011) Astrocytes are important mediators of Abeta-induced neurotoxicity and tau phosphorylation in primary culture. *Cell Death Dis* **2**:e167.
- Gault VA, Porter WD, Flatt PR, and Holscher C (2010) Actions of exendin-4 therapy on cognitive function and hippocampal synaptic plasticity in mice fed a high-fat diet. *Int J Obes (Lond)* **34**:1341–1344.
- Ge YW and Lahiri DK (2002) Regulation of promoter activity of the APP gene by cytokines and growth factors: implications in Alzheimer's disease. *Ann NY Acad Sci* **973**:463–467.
- German JP, Wisse BE, Thaler JP, Oh-I S, Sarruf DA, Ogimoto K, Kaiyala KJ, Fischer JD, Matsen ME, Taborsky GJ Jr, et al. (2010) Leptin deficiency causes insulin resistance induced by uncontrolled diabetes. *Diabetes* **59**:1626–1634.
- Giannessi F, Giambelluca MA, Grasso L, Scavuzzo MC, and Ruffoli R (2008) Curcumin protects Leydig cells of mice from damage induced by chronic alcohol administration. *Med Sci Monit* **14**:BR237–BR242.
- Giroir BP, Horton JW, White DJ, McIntyre KL, and Lin CQ (1994) Inhibition of tumor necrosis factor prevents myocardial dysfunction during burn shock. *Am J Physiol* **267**:H118–H124.
- Goedert M (2004) Tau protein and neurodegeneration. *Semin Cell Dev Biol* **15**:45–49.
- Goldgaber D, Harris HW, Hla T, Maciag T, Donnelly RJ, Jacobsen JS, Vitek MP, and Gajdusek DC (1989) Interleukin 1 regulates synthesis of amyloid beta-protein precursor mRNA in human endothelial cells. *Proc Natl Acad Sci USA* **86**:7606–76010.
- Golovliov I, Kuoppa K, Sjøstedt A, Tarnvik A, and Sandstrom G (1996) Cytokine expression in the liver of mice infected with a highly virulent strain of *Francisella tularensis*. *FEMS Immunol Med Microbiol* **13**:239–244.
- Gonzalez-Gay MA, De Matias JM, Gonzalez-Juanatey C, Garcia-Porrúa C, Sanchez-Andrade A, Martin J, and Llorca J (2006) Anti-tumor necrosis factor-alpha blockade improves insulin resistance in patients with rheumatoid arthritis. *Clin Exp Rheumatol* **24**:83–86.
- Gonzalez-Gay MA, Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA, and Llorca J (2010) Insulin resistance in rheumatoid arthritis: the impact of the anti-TNF-alpha therapy. *Ann NY Acad Sci* **1193**:153–159.
- González-Gay MA, González-Juanatey C, Miranda-Filloy JA, and Llorca J (2012) The potential effect of TNF-alpha antagonist therapy in rheumatoid arthritis may depend on the degree and severity of insulin resistance before the onset of this therapy. *Horm Metab Res* **44**:558–559.
- Goren I, Müller E, Pfeilschifter J, and Frank S (2006) Severely impaired insulin

- signaling in chronic wounds of diabetic ob/ob mice: a potential role of tumor necrosis factor- α . *Am J Pathol* **168**:765–777.
- Gorlovoy P, Larionov S, Pham TT, and Neumann H (2009) Accumulation of tau induced in neurites by microglial proinflammatory mediators. *FASEB J* **23**:2502–2513.
- Götz J, Ittner A, and Ittner LM (2012) Tau-targeted treatment strategies in Alzheimer's disease. *Br J Pharmacol* **165**:1246–1259.
- Greco SJ, Sarkar S, Casadesus G, Zhu X, Smith MA, Ashford JW, Johnston JM, and Tezapsidis N (2009) Leptin inhibits glycogen synthase kinase-3 β to prevent tau phosphorylation in neuronal cells. *Neurosci Lett* **455**:191–194.
- Green RC, Schneider LS, Amato DA, Beelen AP, Wilcock G, Swabb EA, Zavitz KH, and Tarenfluril Phase 3 Study Group (2009) Effect of tarenfluril on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized controlled trial. *JAMA* **302**:2557–2564.
- Greig NH, Giordano T, Zhu X, Yu QS, Perry TA, Holloway HW, Brossi A, Rogers JT, Sambamurti K, and Lahiri DK (2004a) Thalidomide-based TNF- α inhibitors for neurodegenerative diseases. *Acta Neurobiol Exp (Wars)* **64**:1–9.
- Greig NH, Mattson MP, Perry T, Chan SL, Giordano T, Sambamurti K, Rogers JT, Ovadia H, and Lahiri DK (2004b) New therapeutic strategies and drug candidates for neurodegenerative diseases: p53 and TNF- α inhibitors, and GLP-1 receptor agonists. *Ann NY Acad Sci* **1035**:290–315.
- Griffin WS, Stanley LC, Ling C, White L, MacLeod V, Perrot LJ, White CL 3rd, and Araoz C (1989) Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. *Proc Natl Acad Sci USA* **86**:7611–7615.
- Gump FE, Long C, Killian P, and Kinney JM (1974) Studies of glucose intolerance in septic injured patients. *J Trauma* **14**:378–388.
- Hamilton A, Patterson S, Porter D, Gault VA, and Holscher C (2011) Novel GLP-1 mimetics developed to treat type 2 diabetes promote progenitor cell proliferation in the brain. *J Neurosci Res* **89**:481–489.
- Hand CC and Brines M (2011) Promises and pitfalls in erythropoietin-mediated tissue protection: are nonerythropoietic derivatives a way forward? *J Invest Med* **59**:1073–1082.
- Hansen FM, Nilsson P, Sonne O, Hustedt BE, Nilsson-Ehle P, Nielsen JH, and Løvd A (1983) Variations in insulin responsiveness in rat fat cells are due to metabolic differences rather than insulin binding. *Diabetologia* **24**:131–135.
- Hardardóttir I, Kunitake ST, Moser AH, Doerrler WT, Rapp JH, Grünfeld C, and Feingold KR (1994) Endotoxin and cytokines increase hepatic messenger RNA levels and serum concentrations of apolipoprotein J (clusterin) in Syrian hamsters. *J Clin Invest* **94**:1304–1309.
- Hardy J and Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* **297**:353–356.
- Harmsen MM and De Haard HJ (2007) Properties, production, and applications of camelid single-domain antibody fragments. *Appl Microbiol Biotechnol* **77**:13–22.
- Hart BL (1988) Biological basis of the behavior of sick animals. *Neurosci Biobehav Rev* **12**:123–137.
- Härtig W, Stieler J, Boerema AS, Wolf J, Schmidt U, Weissfuss J, Bullmann T, Strijkstra AM, and Arendt T (2007) Hibernation model of tau phosphorylation in hamsters: selective vulnerability of cholinergic basal forebrain neurons - implications for Alzheimer's disease. *Eur J Neurosci* **25**:69–80.
- Hauptmann S, Scherping I, Dröse S, Brandt U, Schulz KL, Jendrach M, Leuner K, Eckert A, and Müller WE (2009) Mitochondrial dysfunction: an early event in Alzheimer pathology accumulates with age in AD transgenic mice. *Neurobiol Aging* **30**:1574–1586.
- Havrankova J, Roth J, and Brownstein M (1978) Insulin receptors are widely distributed in the central nervous system of the rat. *Nature* **272**:827–829.
- He J, Evans CO, Hoffman SW, Oyesiku NM, and Stein DG (2004) Progesterone and allopregnanolone reduce inflammatory cytokines after traumatic brain injury. *Exp Neurol* **189**:404–412.
- Hernández-Caselles T and Stutman O (1993) Immune functions of tumor necrosis factor. I. Tumor necrosis factor induces apoptosis of mouse thymocytes and can also stimulate or inhibit IL-6-induced proliferation depending on the concentration of mitogenic costimulation. *J Immunol* **151**:3999–4012.
- Herold KC, Vezys V, Sun Q, Viktora D, Seung E, Reiner S, and Brown DR (1996) Regulation of cytokine production during development of autoimmune diabetes induced with multiple low doses of streptozotocin. *J Immunol* **156**:3521–3527.
- Hicks SD and Miller MW (2011) Effects of ethanol on transforming growth factor B1-dependent and -independent mechanisms of neural stem cell apoptosis. *Exp Neurol* **229**:372–380.
- Hirota T, Lewis WG, Liu AC, Lee JW, Schultz PG, and Kay SA (2008) A chemical biology approach reveals period shortening of the mammalian circadian clock by specific inhibition of GSK-3 β . *Proc Natl Acad Sci USA* **105**:20746–20751.
- Hoane MR, Kaufman N, Vitek MP, and McKenna SE (2009) COG1410 improves cognitive performance and reduces cortical neuronal loss in the traumatically injured brain. *J Neurotrauma* **26**:121–129.
- Hoeks J, van Herpen NA, Mensink M, Moonen-Kornips E, van Beurden D, Hesselink MK, and Schrauwen P (2010) Prolonged fasting identifies skeletal muscle mitochondrial dysfunction as consequence rather than cause of human insulin resistance. *Diabetes* **59**:2117–2125.
- Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, Jones RW, Bullock R, Love S, Neal JW, et al. (2008) Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. *Lancet* **372**:216–223.
- Hölscher C and Li L (2010) New roles for insulin-like hormones in neuronal signaling and protection: new hopes for novel treatments of Alzheimer's disease? *Neurobiol Aging* **31**:1495–1502.
- Holst JJ, Bureclín R, and Nathanson E (2011) Neuroprotective properties of GLP-1: theoretical and practical applications. *Curr Med Res Opin* **27**:547–558.
- Holstad M and Sandler S (2001) A transcriptional inhibitor of TNF- α prevents diabetes induced by multiple low-dose streptozotocin injections in mice. *J Autoimmun* **16**:441–447.
- Hong M and Lee VM (1997) Insulin and insulin-like growth factor-1 regulate tau phosphorylation in cultured human neurons. *J Biol Chem* **272**:19547–19553.
- Honjo H, Ogino Y, Naitoh K, Urabe M, Kitawaki J, Yasuda J, Yamamoto T, Ishihara S, Okada H, and Yonezawa T (1989) In vivo effects by estrone sulfate on the central nervous system-senile dementia (Alzheimer's type). *J Steroid Biochem* **34**:521–525.
- Hooper C, Killick R, and Lovestone S (2008) The GSK3 hypothesis of Alzheimer's disease. *J Neurochem* **104**:1433–1439.
- Hooper C, Markevich V, Plattner F, Killick R, Schofield E, Engel T, Hernandez F, Anderton B, Rosenblum K, Bliss T, et al. (2007) Glycogen synthase kinase-3 inhibition is integral to long-term potentiation. *Eur J Neurosci* **25**:81–86.
- Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, and Spiegelman BM (1996) IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF- α - and obesity-induced insulin resistance. *Science* **271**:665–668.
- Hotamisligil GS, Shargill NS, and Spiegelman BM (1993) Adipose expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance. *Science* **259**:87–91.
- Hoyer S, Lee SK, Löfler T, and Schliebs R (2000) Inhibition of the neuronal insulin receptor. An in vivo model for sporadic Alzheimer disease? *Ann NY Acad Sci* **920**:256–258.
- Hoyer S, Müller D, and Plaschke K (1994) Desensitization of brain insulin receptor. Effect on glucose/energy and related metabolism. *J Neural Transm Suppl* **44**:259–268.
- Hsu SM, Chen YC, and Jiang MC (2000) 17 beta-estradiol inhibits tumor necrosis factor- α -induced nuclear factor-kappa B activation by increasing nuclear factor-kappa B p105 level in MCF-7 breast cancer cells. *Biochem Biophys Res Commun* **279**:47–52.
- Hu S, Begum AN, Jones MR, Oh MS, Beech WK, Beech BH, Yang F, Chen P, Ubeda OJ, Kim PC, et al. (2009) GSK3 inhibitors show benefits in an Alzheimer's disease (AD) model of neurodegeneration but adverse effects in control animals. *Neurobiol Dis* **33**:193–206.
- Huang X, Cuajungco MP, Atwood CS, Hartshorn MA, Tyndall JD, Hanson GR, Stokes KC, Leopold M, Multhaup G, Goldstein LE, et al. (1999) Cu(II) potentiation of Alzheimer Abeta neurotoxicity. Correlation with cell-free hydrogen peroxide production and metal reduction. *J Biol Chem* **274**:37111–37116.
- Hung LW, Ciccostoto GD, Giannakis E, Tew DJ, Perez K, Masters CL, Cappai R, Wade JD, and Barnham KJ (2008) Amyloid-beta peptide (Abeta) neurotoxicity is modulated by the rate of peptide aggregation: Abeta dimers and trimers correlate with neurotoxicity. *J Neurosci* **28**:11950–11958.
- Ichihama T, Hayashi T, and Furukawa S (1996) Cerebrospinal fluid concentrations of soluble tumor necrosis factor receptor in bacterial and aseptic meningitis. *Neurology* **46**:837–838.
- Idro R, Kakooza-Mwesige A, Balyejussa S, Mirembe G, Mugasha C, Tugumisirize J, and Byarugaba J (2010) Severe neurological sequelae and behaviour problems after cerebral malaria in Ugandan children. *BMC Res Notes* **3**:104.
- Itaka C, Miyazaki K, Akaike T, and Ishida N (2005) A role for glycogen synthase kinase-3 β in the mammalian circadian clock. *J Biol Chem* **280**:29397–29402.
- Iqbal J, Sun L, Kumar TR, Blair HC, and Zaidi M (2006) Follicle-stimulating hormone stimulates TNF production from immune cells to enhance osteoblast and osteoclast formation. *Proc Natl Acad Sci USA* **103**:14925–14930.
- Irving EA, Nicoll J, Graham DI, and Dewar D (1996) Increased tau immunoreactivity in oligodendrocytes following human stroke and head injury. *Neurosci Lett* **213**:189–192.
- Isik AT, Celik T, Ulusoy G, Onguru O, Elibol B, Doruk H, Bozoglu E, Kayir H, Mas MR, and Akman S (2009) Curcumin ameliorates impaired insulin/IGF signalling and memory deficit in a streptozotocin-treated rat model. *Age* **31**:39–49.
- Islander U, Jochems C, Lagerquist MK, Forsblad-d'Elia H, and Carlsten H (2011) Estrogens in rheumatoid arthritis; the immune system and bone. *Mol Cell Endocrinol* **335**:14–29.
- Jana M, Palencia CA, and Pahan K (2008) Fibrillar amyloid-beta peptides activate microglia via TLR2: implications for Alzheimer's disease. *J Immunol* **181**:7254–7262.
- Jiang C, Wang J, Li X, Liu C, Chen N, and Hao Y (2009) Progesterone exerts neuroprotective effects by inhibiting inflammatory response after stroke. *Inflamm Res* **58**:619–624.
- John CC, Bangirana P, Byarugaba J, Opoka RO, Idro R, Jurek AM, Wu B, and Boivin MJ (2008a) Cerebral malaria in children is associated with long-term cognitive impairment. *Pediatrics* **122**:e92–e99.
- John CC, Kutamba E, Mugarura K, and Opoka RO (2010) Adjunctive therapy for cerebral malaria and other severe forms of Plasmodium falciparum malaria. *Expert Rev Anti Infect Ther* **8**:997–1008.
- John CC, Panoskantis-Mortari A, Opoka RO, Park GS, Orchard PJ, Jurek AM, Idro R, Byarugaba J, and Boivin MJ (2008b) Cerebrospinal fluid cytokine levels and cognitive impairment in cerebral malaria. *Am J Trop Med Hyg* **78**:198–205.
- Jolivald CG, Lee CA, Beiswenger KK, Smith JL, Orlov M, Torrance MA, and Masliah E (2008) Defective insulin signaling pathway and increased glycogen synthase kinase-3 activity in the brain of diabetic mice: parallels with Alzheimer's disease and correction by insulin. *J Neurosci Res* **86**:3265–3274.
- Jope RS and Johnson GV (2004) The glamour and gloom of glycogen synthase kinase-3. *Trends Biochem Sci* **29**:95–102.
- Junod A, Lambert AE, Orci L, Pictet R, Gonet AE, and Renold AE (1967) Studies of the diabetogenic action of streptozotocin. *Proc Soc Exp Biol Med* **126**:201–205.
- Kaiser K, Texier A, Ferrandiz J, Buguet A, Meiller A, Latour C, Peyron F, Cesuglio R, and Pictot S (2006) Recombinant human erythropoietin prevents the death of mice during cerebral malaria. *J Infect Dis* **193**:987–995.
- Kaneko I, Yamada N, Sakuraba Y, Kamenosono M, and Tutumi S (1995) Suppression of mitochondrial succinate dehydrogenase, a primary target of beta-amyloid, and its derivative racemized at Ser residue. *J Neurochem* **65**:2585–2593.
- Kanik KS and Wilder RL (2000) Hormonal alterations in rheumatoid arthritis, including the effects of pregnancy. *Rheum Dis Clin North Am* **26**:805–823.
- Karatsoreos IN, Butler MP, Lesauter J, and Silver R (2011) Androgens modulate

- structure and function of the suprachiasmatic nucleus brain clock. *Endocrinology* **152**:1970–1978.
- Karran E, Mercken M, and De Strooper B (2011) The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nat Rev Drug Discov* **10**:698–712.
- Käss AS, Lea TE, Torjesen PA, Gulseth HC, and Førre ØT (2010) The association of luteinizing hormone and follicle-stimulating hormone with cytokines and markers of disease activity in rheumatoid arthritis: a case-control study. *Scand J Rheumatol* **39**:109–117.
- Kaufman NA, Beare JE, Tan AA, Vitek MP, McKenna SE, and Hoane MR (2010) COG1410, an apolipoprotein E-based peptide, improves cognitive performance and reduces cortical loss following moderate fluid percussion injury in the rat. *Behav Brain Res* **214**:395–401.
- Kaushal V and Schlichter LC (2008) Mechanisms of microglia-mediated neurotoxicity in a new model of the stroke penumbra. *J Neurosci* **28**:2221–2230.
- Kayal RA, Ablow J, McKenzie E, Krothapalli N, Silkman L, Gerstenfeld L, Einhorn TA, and Graves DT (2009) Diabetes causes the accelerated loss of cartilage during fracture repair which is reversed by insulin treatment. *Bone* **44**:357–363.
- Kern W, Born J, Schreiber H, and Fehm HL (1999) Central nervous system effects of intranasally administered insulin during euglycemia in men. *Diabetes* **48**:557–563.
- Ketterer C, Tschritter O, Preissl H, Heni M, Häring HU, and Fritsche A (2011) Insulin sensitivity of the human brain. *Diabetes Res Clin Pract* **93** (Suppl 1):S47–S51.
- Khan KN, Kitajima M, Hiraki K, Fujishita A, Sekine I, Ishimaru T, and Masuzaki H (2010) Changes in tissue inflammation, angiogenesis and apoptosis in endometriosis, adenomyosis and uterine myoma after GnRH agonist therapy. *Hum Reprod* **25**:642–653.
- Kihara M, Carter JA, Holding PA, Vargha-Khadem F, Scott RC, Idro R, Fegan GW, de Haan M, Neville BG, and Newton CR (2009) Impaired everyday memory associated with encephalopathy of severe malaria: the role of seizures and hippocampal damage. *Malar J* **8**:273.
- Kim YJ and Jung YW (2010) Systemic injection of recombinant human erythropoietin after focal cerebral ischemia enhances oligodendroglial and endothelial progenitor cells in rat brain. *Acta Cell Biol* **43**:140–149.
- Kimiwada T, Sakurai M, Ohashi H, Aoki S, Tominaga T, and Wada K (2009) Clock genes regulate neurogenic transcription factors, including NeuroD1, and the neuronal differentiation of adult neural stem/progenitor cells. *Neurochem Int* **54**:277–285.
- Kimura T, Yamashita S, Nakao S, Park JM, Murayama M, Mizoroki T, Yoshiike Y, Sahara N, and Takashima A (2008) GSK-3beta is required for memory reconsolidation in adult brain. *PLoS One* **3**:e3540.
- Kiortsis DN, Mavridis AK, Vasakos S, Nikas SN, and Drosos AA (2005) Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. *Ann Rheum Dis* **64**:765–766.
- Kipp M, Karakaya S, Johann S, Kampmann E, Mey J, and Beyer C (2007) Oestrogen and progesterone reduce lipopolysaccharide-induced expression of tumour necrosis factor-alpha and interleukin-18 in midbrain astrocytes. *J Neuroendocrinol* **19**:819–822.
- Kitazawa M, Cheng D, Tsukamoto MR, Koike MA, Wes PD, Vasilevko V, Cribbs DH, and LaFerla FM (2011) Blocking IL-1 signaling rescues cognition, attenuates tau pathology, and restores neuronal beta-catenin pathway function in an Alzheimer's disease model. *J Immunol* **187**:6539–6549.
- Knauf C, Cani PD, Ait-Belgnaoui A, Benani A, Dray C, Cabou C, Colom A, Uldry M, Rastrelli S, Sabatier E, et al. (2008) Brain glucagon-like peptide 1 signaling controls the onset of high-fat diet-induced insulin resistance and reduces energy expenditure. *Endocrinology* **149**:4768–4777.
- Ko HW, Kim EY, Chiu J, Vanselow JT, Kramer A, and Edery I (2010) A hierarchical phosphorylation cascade that regulates the timing of PERIOD nuclear entry reveals novel roles for proline-directed kinases and GSK-3beta/SGG in circadian clocks. *J Neurosci* **30**:12664–12675.
- Koch C, Augustine RA, Steger J, Ganjam GK, Benzler J, Pracht C, Lowe C, Schwartz MW, Shepherd PR, Anderson GM, et al. (2010) Leptin rapidly improves glucose homeostasis in obese mice by increasing hypothalamic insulin sensitivity. *J Neurosci* **30**:16180–16187.
- Kohsaka A and Bass J (2007) A sense of time: how molecular clocks organize metabolism. *Trends Endocrinol Metab* **18**:4–11.
- Koopmans SJ, Mroz Z, Dekker R, Corbijn H, Ackermans M, and Sauerwein H (2006) Association of insulin resistance with hyperglycemia in streptozotocin-diabetic pigs: effects of metformin at isoenergetic feeding in a type 2-like diabetic pig model. *Metabolism* **55**:960–971.
- Kozikowski AP, Gunosewoyo H, Guo S, Gaisina IN, Walter RL, Ketcherside A, McClung CA, Mesecar AD, and Caldaroni B (2011) Identification of a glycogen synthase kinase-3beta inhibitor that attenuates hyperactivity in CLOCK mutant mice. *ChemMedChem* **6**:1593–1602.
- Kristensson K, Nygård M, Bertini G, and Bentivoglio M (2010) African trypanosome infections of the nervous system: parasite entry and effects on sleep and synaptic functions. *Prog Neurobiol* **91**:152–171.
- Kruman II, Nath A, Maragos WF, Chan SL, Jones M, Rangnekar VM, Jakel RJ, and Mattson MP (1999) Evidence that Par-4 participates in the pathogenesis of HIV encephalitis. *Am J Pathol* **155**:39–46.
- Kuriyama K, Sasahara K, Kudo T, and Shibata S (2004) Daily injection of insulin attenuated impairment of liver circadian clock oscillation in the streptozotocin-treated diabetic mouse. *FEBS Lett* **572**:206–210.
- Lang CH and Dobrescu C (1989) In vivo insulin resistance during nonlethal hypermetabolic sepsis. *Circ Shock* **28**:165–178.
- Lang CH, Dobrescu C, and Bagby GJ (1992) Tumor necrosis factor impairs insulin action on peripheral glucose disposal and hepatic glucose output. *Endocrinology* **130**:43–52.
- Laskowitz DT, Goel S, Bennett ER, and Matthew WD (1997) Apolipoprotein E suppresses glial cell secretion of TNF-alpha. *J Neuroimmunol* **76**:70–74.
- Laskowitz DT, McKenna SE, Song P, Wang H, Durham L, Yeung N, Christensen D, and Vitek MP (2007) COG1410, a novel apolipoprotein E-based peptide, improves functional recovery in a murine model of traumatic brain injury. *J Neurotrauma* **24**:1093–1107.
- Laskowitz DT, Thekdi AD, Thekdi SD, Han SK, Myers JK, Pizzo SV, and Bennett ER (2001) Downregulation of microglial activation by apolipoprotein E and apoE-mimetic peptides. *Exp Neurol* **167**:74–85.
- Laurin D, David Curb J, Masaki KH, White LR, and Launer LJ (2009) Midlife C-reactive protein and risk of cognitive decline: a 31-year follow-up. *Neurobiol Aging* **30**:1724–1727.
- Leconte C, Bihel E, Lepelletier FX, Bouët V, Saulnier R, Petit E, Boulouard M, Bernaudin M, and Schumann-Bard P (2011) Comparison of the effects of erythropoietin and its carbamylated derivative on behaviour and hippocampal neurogenesis in mice. *Neuropharmacology* **60**:354–364.
- Lee SM, Yune TY, Kim SJ, Kim YC, Oh YJ, Markelonis GJ, and Oh TH (2004) Minocycline inhibits apoptotic cell death via attenuation of TNF-alpha expression following iNOS/NO induction by lipopolysaccharide in neuron/glia co-cultures. *J Neurochem* **91**:568–578.
- Lei P, Ayton S, Bush AI, and Adlard PA (2011) GSK-3 in neurodegenerative diseases. *Int J Alzheimers Dis* **2011**:189246.
- LeRoith D, Lesniak MA, and Roth J (1981a) Insulin in insects and annelids. *Diabetes* **30**:70–76.
- LeRoith D, Shiloach J, Roth J, and Lesniak MA (1981b) Insulin or a closely related molecule is native to *Escherichia coli*. *J Biol Chem* **256**:6533–6536.
- Lester-Coll N, Rivera EJ, Soscia SJ, Doiron K, Wands JR, and de la Monte SM (2006) Intracerebral streptozotocin model of type 3 diabetes: relevance to sporadic Alzheimer's disease. *J Alzheimers Dis* **9**:13–33.
- Ley EJ, Srour MK, Clond MA, Barnajian M, Tillou A, Mirocha J, and Salim A (2011) Diabetic patients with traumatic brain injury: insulin deficiency is associated with increased mortality. *J Trauma* **70**:1141–1144.
- Li G, Barrett EJ, Barrett MO, Cao W, and Liu Z (2007) Tumor necrosis factor-alpha induces insulin resistance in endothelial cells via a p38 mitogen-activated protein kinase-dependent pathway. *Endocrinology* **148**:3356–3363.
- Li L, El-Kholy W, Rhodes CJ, and Brubaker PL (2005) Glucagon-like peptide-1 protects beta cells from cytokine-induced apoptosis and necrosis: role of protein kinase B. *Diabetologia* **48**:1339–1349.
- Li X and Jope RS (2010) Is glycogen synthase kinase-3 a central modulator in mood regulation? *Neuropsychopharmacology* **35**:2143–2154.
- Li Y, Duffy KB, Ottlinger MA, Ray B, Bailey JA, Holloway HW, Tweedie D, Perry T, Mattson MP, Kapogiannis D, et al. (2010) GLP-1 receptor stimulation reduces amyloid-beta peptide accumulation and cytotoxicity in cellular and animal models of Alzheimer's disease. *J Alzheimers Dis* **19**:1205–1219.
- Liao YF, Wang BJ, Cheng HT, Kuo LH, and Wolfe MS (2004) Tumor necrosis factor-alpha, interleukin-1beta, and interferon-gamma stimulate gamma-secretase-mediated cleavage of amyloid precursor protein through a JNK-dependent MAPK pathway. *J Biol Chem* **279**:49523–49532.
- Lieb W, Beiser AS, Vasan RS, Tan ZS, Au R, Harris TB, Roubenoff R, Auerbach S, DeCarli C, Wolf PA, et al. (2009) Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. *JAMA* **302**:2565–2572.
- Liesz A, Suri-Payer E, Veltkamp C, Doerr H, Sommer C, Rivest S, Giese T, and Veltkamp R (2009) Regulatory T cells are key cerebroprotective immunomodulators in acute experimental stroke. *Nat Med* **15**:192–199.
- Lin CY, Higginbotham DA, Judd RL, and White BD (2002) Central leptin increases insulin sensitivity in streptozotocin-induced diabetic rats. *Am J Physiol Endocrinol Metab* **282**:E1084–E1091.
- Lin J, Li X, Yuan F, Lin L, Cook CL, Rao ChV, and Lei Z (2010) Genetic ablation of luteinizing hormone receptor improves the amyloid pathology in a mouse model of Alzheimer disease. *J Neuropathol Exp Neurol* **69**:253–261.
- Liu H, Dear AE, Knudsen LB, and Simpson RW (2009) A long-acting glucagon-like peptide-1 analogue attenuates induction of plasminogen activator inhibitor type-1 and vascular adhesion molecules. *J Endocrinol* **201**:59–66.
- Liu Y, Liu F, Grundke-Iqbal I, Iqbal K, and Gong CX (2011) Deficient brain insulin signalling pathway in Alzheimer's disease and diabetes. *J Pathol* **225**:54–62.
- London ED, Berman SM, Chakrapani S, Delibasi T, Monterosso J, Erol HK, Paz-Filho G, Wong ML, and Licinio J (2011) Short-term plasticity of gray matter associated with leptin deficiency and replacement. *J Clin Endocrinol Metab* **96**:E1212–E1220.
- Lorenzo M, Fernández-Veledo S, Vila-Bedmar R, Garcia-Guerra L, De Alvaro C, and Nieto-Vazquez I (2008) Insulin resistance induced by tumor necrosis factor-alpha in myocytes and brown adipocytes. *J Anim Sci* **86**:E94–E104.
- Lovestone S and Reynolds CH (1997) The phosphorylation of tau: a critical stage in neurodevelopment and neurodegenerative processes. *Neuroscience* **78**:309–324.
- Lovestone S, Reynolds CH, Latimer D, Davis DR, Anderton BH, Gallo JM, Hanger D, Mulot S, Marquardt B, and Stabel S (1994) Alzheimer's disease-like phosphorylation of the microtubule-associated protein tau by glycogen synthase kinase-3 in transfected mammalian cells. *Curr Biol* **4**:1077–1086.
- Lynch JR, Morgan D, Mance J, Matthew WD, and Laskowitz DT (2001) Apolipoprotein E modulates glial activation and the endogenous central nervous system inflammatory response. *J Neuroimmunol* **114**:107–113.
- Lynch JR, Wang H, Mace B, Leinenweber S, Warner DS, Bennett ER, Vitek MP, McKenna S, and Laskowitz DT (2005) A novel therapeutic derived from apolipoprotein E reduces brain inflammation and improves outcome after closed head injury. *Exp Neurol* **192**:109–116.
- Maegraith BG (1954) Physiological aspects of protozoan infection. *Annu Rev Microbiol* **8**:273–288.
- Mandelkow EM, Drewes G, Biernat J, Gustke N, Van Lint J, Vandenheede JR, and Mandelkow E (1992) Glycogen synthase kinase-3 and the Alzheimer-like state of microtubule-associated protein tau. *FEBS Lett* **314**:315–321.
- Martin M, Rehani K, Jope RS, and Michalek SM (2005) Toll-like receptor-mediated cytokine production is differentially regulated by glycogen synthase kinase 3. *Nat Immunol* **6**:777–784.

- Marwarha G, Dasari B, Prabhakara JP, Schommer J, and Ghribi O (2010) β -Amyloid regulates leptin expression and tau phosphorylation through the mTORC1 signaling pathway. *J Neurochem* **115**:373–384.
- Mastroianni CM, Paoletti F, Massetti AP, Falciano M, and Vullo V (1990) Elevated levels of tumor necrosis factor (TNF) in the cerebrospinal fluid from patients with HIV-associated neurological disorders. *Acta Neurol Napoli* **12**:66–67.
- Matsuo T, Yamaguchi S, Mitsui S, Emi A, Shimoda F, and Okamura H (2003) Control mechanism of the circadian clock for timing of cell division in vivo. *Science* **302**:255–259.
- Mayordomo L, Marengo JL, Gomez-Mateos J, and Rejon E (2002) Pulmonary miliary tuberculosis in a patient with anti-TNF-alpha treatment. *Scand J Rheumatol* **31**:44–45.
- McAlpine FE, Lee JK, Harms AS, Ruhn KA, Blurton-Jones M, Hong J, Das P, Golde TE, LaFerla FM, Oddo S, et al. (2009) Inhibition of soluble TNF signaling in a mouse model of Alzheimer's disease prevents pre-plaque amyloid-associated neuropathology. *Neurobiol Dis* **34**:163–177.
- McCall JL, Tuckey JA, and Parry BR (1992) Serum tumour necrosis factor alpha and insulin resistance in gastrointestinal cancer. *Br J Surg* **79**:1361–1363.
- McClean PL, Parthasarathy V, Faivre E, and Höltscher C (2011) The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. *J Neurosci* **31**:6587–6594.
- McConnell SE, Alla J, Wheat E, Romeo RD, McEwen B, and Thornton JE (2012) The role of testicular hormones and luteinizing hormone in spatial memory in adult male rats. *Horm Behav* **61**:479–486.
- McGeer PL and McGeer EG (1995) The inflammatory response system of brain: implications for therapy of Alzheimer and other neurodegenerative diseases. *Brain Res Rev* **21**:195–218.
- McNay EC and Recknagel AK (2011) Brain insulin signaling: a key component of cognitive processes and a potential basis for cognitive impairment in type 2 diabetes. *Neurobiol Learn Mem* **96**:432–442.
- Medana IM, Day NP, Hien TT, Mai NT, Bethell D, Phu NH, Farrar J, Esiri MM, White NJ, and Turner GD (2002) Axonal injury in cerebral malaria. *Am J Pathol* **160**:655–666.
- Medana IM, Idro R, and Newton CR (2007) Axonal and astrocyte injury markers in the cerebrospinal fluid of Kenyan children with severe malaria. *J Neurol Sci* **258**:93–98.
- Medana IM, Lindert RB, Wurster U, Hien TT, Day NP, Phu NH, Mai NT, Chuong LV, Chau TT, Turner GD, et al. (2005) Cerebrospinal fluid levels of markers of brain parenchymal damage in Vietnamese adults with severe malaria. *Trans R Soc Trop Med Hyg* **99**:610–617.
- Meistrell ME 3rd, Botchkina GI, Wang H, Di Santo E, Cockcroft KM, Bloom O, Vishnubhakt JM, Ghezzi P, and Tracey KJ (1997) Tumor necrosis factor is a brain damaging cytokine in cerebral ischemia. *Shock* **8**:341–348.
- Mela LM, Miller LD, Bacalzo LV Jr, Olofsson K, and White RR 4th (1972) Alterations of mitochondrial structure and energy-linked functions in hemorrhagic shock and endotoxemia. *Adv Exp Med Biol* **33**:231–242.
- Mengatto CM, Mussano F, Honda Y, Colwell CS, and Nishimura I (2011) Circadian rhythm and cartilage extracellular matrix genes in osseointegration: a genome-wide screening of implant failure by vitamin D deficiency. *PLoS One* **6**:e15848.
- Mensah-Brown EP, Obineche EN, Galadari S, Chandranath E, Shahin A, Ahmed I, Patel SM, and Adem A (2005) Streptozotocin-induced diabetic nephropathy in rats: the role of inflammatory cytokines. *Cytokine* **31**:180–190.
- Meresman GF, Bilotas MA, Lombardi E, Tesone M, Sueldo C, and Barañao RI (2003) Effect of GnRH analogues on apoptosis and release of interleukin-1beta and vascular endothelial growth factor in endometrial cell cultures from patients with endometriosis. *Hum Reprod* **18**:1767–1771.
- Moe GW, Marin-Garcia J, Konig A, Goldenthal M, Lu X, and Feng Q (2004) In vivo TNF-alpha inhibition ameliorates cardiac mitochondrial dysfunction, oxidative stress, and apoptosis in experimental heart failure. *Am J Physiol Heart Circ Physiol* **287**:H1813–H1820.
- Moriya T, Hiraishi K, Horie N, Mitome M, and Shinohara K (2007) Correlative association between circadian expression of mousePer2 gene and the proliferation of the neural stem cells. *Neuroscience* **146**:494–498.
- Mowery NT, Gunter OL, Guillaumonjeu O, Dossett LA, Dortch MJ, Morris JA Jr, and May AK (2009) Stress insulin resistance is a marker for mortality in traumatic brain injury. *J Trauma* **66**:145–151.
- Mueller L, von Seggern L, Schumacher J, Goumas F, Wilms C, Braun F, and Broering DC (2010) TNF-alpha similarly induces IL-6 and MCP-1 in fibroblasts from colorectal liver metastases and normal liver fibroblasts. *Biochem Biophys Res Commun* **397**:586–591.
- Murphy VA and Johanson CE (1985) Adrenergic-induced enhancement of brain barrier system permeability to small nonelectrolytes: choroid plexus versus cerebral capillaries. *J Cereb Blood Flow Metab* **5**:401–412.
- Nairz M, Schroll A, Moschen AR, Sonnweber T, Theurl M, Theurl I, Taub N, Jamnig C, Neurauter D, Huber LA, et al. (2011) Erythropoietin contrastingly affects bacterial infection and experimental colitis by inhibiting nuclear factor-kappaB-inducible immune pathways. *Immunity* **34**:61–74.
- Nairz M, Sonnweber T, Schroll A, Theurl I, and Weiss G (2012) The pleiotropic effects of erythropoietin in infection and inflammation. *Microbes Infect* **14**:238–246.
- Nakamura TJ, Sellix MT, Kudo T, Nakao N, Yoshimura T, Ebihara S, Colwell CS, and Block GD (2010) Influence of the estrous cycle on clock gene expression in reproductive tissues: effects of fluctuating ovarian steroid hormone levels. *Steroids* **75**:203–212.
- Nakamura TJ, Sellix MT, Menaker M, and Block GD (2008) Estrogen directly modulates circadian rhythms of PER2 expression in the uterus. *Am J Physiol Endocrinol Metab* **295**:E1025–E1031.
- Natalicchio A, De Stefano F, Orlandi MR, Melchiorre M, Leonardini A, Cignarelli A, Labarbuta R, Marchetti P, Perrini S, Laviola L, et al. (2010) Exendin-4 prevents c-Jun N-terminal protein kinase activation by tumor necrosis factor-alpha (TNF-alpha) and inhibits TNF-alpha-induced apoptosis in insulin-secreting cells. *Endocrinology* **151**:2019–2029.
- Nathan C (1989) Secretory products of macrophages. *J Clin Immunol* **79**:319–326.
- Nathoo N, Caris EC, Wiener JA, and Mendel E (2011) History of the vertebral venous plexus and the significant contributions of Breschet and Batson. *Neurosurgery* **69**:1007–1014.
- Navarro JF, Milena FJ, Mora C, Leon C, Claverie F, Flores C, and Garcia J (2005) Tumor necrosis factor-alpha gene expression in diabetic nephropathy: relationship with urinary albumin excretion and effect of angiotensin-converting enzyme inhibition. *Kidney Int Suppl* **(99)**:S98–S102.
- Nieto-Vazquez I, Fernández-Veledo S, de Alvaro C, Rondinone CM, Valverde AM, and Lorenzo M (2007) Protein-tyrosine phosphatase 1B-deficient myocytes show increased insulin sensitivity and protection against tumor necrosis factor-alpha-induced insulin resistance. *Diabetes* **56**:404–413.
- Nihashi T, Inao S, Kajita Y, Kawai T, Sugimoto T, Niwa M, Kabeya R, Hata N, Hayashi S, and Yoshida J (2001) Expression and distribution of beta amyloid precursor protein and beta amyloid peptide in reactive astrocytes after transient middle cerebral artery occlusion. *Acta Neurochir (Wien)* **143**:287–295.
- Noble W, Garwood C, Stephenson J, Kinsey AM, Hanger DP, and Anderton BH (2009) Minocycline reduces the development of abnormal tau species in models of Alzheimer's disease. *FASEB J* **23**:739–750.
- Nothing T, Lindecke A, Koutsilieri E, Maschke M, Husstedt IW, Sopper S, Stüve O, Hartung HP, Arendt G, and Competence Network M (2009) Measurement of soluble inflammatory mediators in cerebrospinal fluid of human immunodeficiency virus-positive patients at distinct stages of infection by solid-phase protein array. *J Neurovirol* **15**:390–400.
- Olgiati P, Politis AM, Papadimitriou GN, De Ronchi D, and Serretti A (2011) Genetics of late-onset Alzheimer's disease: update from the alzgene database and analysis of shared pathways. *Int J Alzheimer's Dis* **2011**:832379.
- Onishi T, Iwashita H, Uno Y, Kunitomo J, Saitoh M, Kimura E, Fujita H, Uchiyama N, Kori M, and Takizawa M (2011) A novel glycogen synthase kinase-3 inhibitor 2-methyl-5-(3-(4-((S)-methylsulfinyl)phenyl)-1-benzofuran-5-yl)-1,3,4-oxadiazole decreases tau phosphorylation and ameliorates cognitive deficits in a transgenic model of Alzheimer's disease. *J Neurochem* **119**:1330–1340.
- Ordóñez P, Moreno M, Alonso A, Llana P, Díaz F, and González C (2008) 17beta-Estradiol and/or progesterone protect from insulin resistance in STZ-induced diabetic rats. *J Steroid Biochem Mol Biol* **111**:287–294.
- Osredkar D, Sall JW, Bickler PE, and Ferriero DM (2010) Erythropoietin promotes hippocampal neurogenesis in *in vitro* models of neonatal stroke. *Neurobiol Dis* **38**:259–265.
- Ostensen M, Aune B, and Husby G (1983) Effect of pregnancy and hormonal changes on the activity of rheumatoid arthritis. *Scand J Rheumatol* **12**:69–72.
- Ott V, Benedict C, Schultes B, Born J, and Hallschmid M (2011) Intranasal administration of insulin to the brain impacts cognitive function and peripheral metabolism. *Diabetes Obes Metab* **14**:214–221.
- Pajak B, Orzechowska S, Pijet B, Pijet M, Pogorzelska A, Gajkowska B, and Orzechowski A (2008) Crossroads of cytokine signaling—the chase to stop muscle cachexia. *J Physiol Pharmacol* **59** (Suppl 9):251–264.
- Paolino D, Cosco D, Molinaro R, Celia C, and Fresta M (2011) Supramolecular devices to improve the treatment of brain diseases. *Drug Discov Today* **16**:311–324.
- Pardridge WM (2010) Biologic TNF-alpha-inhibitors that cross the human blood-brain barrier. *Bioeng Bugs* **1**:231–234.
- Patel NS, Collino M, Yaqoob MM, and Thiemermann C (2011a) Erythropoietin in the intensive care unit: beyond treatment of anemia. *Ann Intensive Care* **1**:40.
- Patel NS, Nandra KK, Brines M, Collino M, Wong WF, Kapoor A, Benetti E, Goh FY, Fantozzi R, Cerami A, et al. (2011b) A nonerythropoietic peptide that mimics the 3D structure of erythropoietin reduces organ injury/dysfunction and inflammation in experimental hemorrhagic shock. *Mol Med* **17**:883–892.
- Paz-Filho G, Wong ML, and Licinio J (2010a) Leptin levels and Alzheimer disease. *JAMA* **303**:1478.
- Paz-Filho G, Wong ML, and Licinio J (2010b) The procognitive effects of leptin in the brain and their clinical implications. *Int J Clin Pract* **64**:1808–1812.
- Pekala P, Kawakami M, Vine W, Lane MD, and Cerami A (1983) Studies of insulin resistance in adipocytes induced by macrophage mediator. *J Exp Med* **157**:1360–1365.
- Peng J, Xie L, Stevenson FF, Melov S, Di Monte DA, and Andersen JK (2006) Nigrostriatal dopaminergic neurodegeneration in the weaver mouse is mediated via neuroinflammation and alleviated by minocycline administration. *J Neurosci* **26**:11644–11651.
- Perry T, Lahiri DK, Sambamurti K, Chen D, Mattson MP, Egan JM, and Greig NH (2003) Glucagon-like peptide-1 decreases endogenous amyloid-beta peptide (Abeta) levels and protects hippocampal neurons from death induced by Abeta and iron. *J Neurosci Res* **72**:603–612.
- Perry VH, Cunningham C, and Holmes C (2007) Systemic infections and inflammation affect chronic neurodegeneration. *Nat Rev Immunol* **7**:161–167.
- Petit-Paitel A, Brau F, Cazareth J, and Chabry J (2009) Involvement of cytosolic and mitochondrial GSK-3beta in mitochondrial dysfunction and neuronal cell death of MPTP/MPP-treated neurons. *PLoS One* **4**:e5491.
- Pickering M, Cumiskey D, and O'Connor JJ (2005) Actions of TNF-alpha on glutamatergic synaptic transmission in the central nervous system. *Exp Physiol* **90**: 663–670.
- Picot S, Bienvenu AL, Konate S, Sissoko S, Barry A, Diarra E, Bamba K, Djimé A, and Doumo OK (2009) Safety of epoetin beta-quinine drug combination in children with cerebral malaria in Mali. *Malar J* **8**:169.
- Plaschke K and Hoyer S (1993) Action of the diabetogenic drug streptozotocin on glycolytic and glycogenolytic metabolism in adult rat brain cortex and hippocampus. *Int J Dev Neurosci* **11**:477–483.
- Porter DW, Kerr BD, Flatt PR, Holscher C, and Gault VA (2010) Four weeks administration of Liraglutide improves memory and learning as well as glycaemic

- control in mice with high fat dietary-induced obesity and insulin resistance. *Diabetes Obes Metab* **12**:891–899.
- Qin B, Qiu W, Avramoglu RK, and Adeli K (2007) Tumor necrosis factor- α induces intestinal insulin resistance and stimulates the overproduction of intestinal apolipoprotein B48-containing lipoproteins. *Diabetes* **56**:450–461.
- Qin L, He J, Hanes RN, Pluzarev O, Hong JS, and Crews FT (2008) Increased systemic and brain cytokine production and neuroinflammation by endotoxin following ethanol treatment. *J Neuroinflammation* **5**:10.
- Quan N, Mhlanga JD, Whiteside MB, McCoy AN, Kristensson K, and Herkenham M (1999) Chronic overexpression of proinflammatory cytokines and histopathology in the brains of rats infected with *Trypanosoma brucei*. *J Comp Neurol* **414**:114–130.
- Ramirez R, Carracedo J, Noguerras S, Buendia P, Merino A, Cañadillas S, Rodríguez M, Tetta C, Martin-Malo A, and Aljama P (2009) Carbamylated darbepoetin derivative prevents endothelial progenitor cell damage with no effect on angiogenesis. *J Mol Cell Cardiol* **47**:781–788.
- Ranges GE, Zlotnik A, Espevik T, Dinarello CA, Cerami A, and Palladino MA Jr (1988) Tumor necrosis factor α /cachectin is a growth factor for thymocytes. Synergistic interactions with other cytokines. *J Exp Med* **167**:1472–1478.
- Rao SC, Li X, Rao ChV, and Magnuson DS (2003) Human chorionic gonadotropin/luteinizing hormone receptor expression in the adult rat spinal cord. *Neurosci Lett* **336**:135–138.
- Ratai EM, Bombardier JP, Joo CG, Annamalai L, Burdo TH, Campbell J, Fell R, Hakimelahi R, He J, Autissier P, et al. (2010) Proton magnetic resonance spectroscopy reveals neuroprotection by oral minocycline in a nonhuman primate model of accelerated NeuroAIDS. *PLoS One* **5**:e10523.
- Raymond RM (1984) Skeletal muscle metabolism and insulin resistance during endotoxin shock in the dog. *Am J Emerg Med* **2**:45–59.
- Raymond RM, McLane MP, Law WR, King NF, and Leutz DW (1988) Myocardial insulin resistance during acute endotoxin shock in dogs. *Diabetes* **37**:1684–1688.
- Rebel VI, Hartnett S, Hill GR, Lazo-Kallanian SB, Ferrara JL, and Sieff CA (1999) Essential role for the p55 tumor necrosis factor receptor in regulating hematopoiesis at a stem cell level. *J Exp Med* **190**:1493–1504.
- Rector RS, Thyfault JP, Uptergrove GM, Morris EM, Naples SP, Borengasser SJ, Mikus CR, Laye MJ, Laughlin MH, Booth FW, et al. (2010) Mitochondrial dysfunction precedes insulin resistance and hepatic steatosis and contributes to the natural history of non-alcoholic fatty liver disease in an obese rodent model. *J Hepatol* **52**:727–736.
- Redl H, Schlag G, Paul E, Bahrami S, Buurman WA, Strieter RM, Kunkel SL, Davies J, and Foulkes R (1996) Endogenous modulators of TNF and IL-1 response are under partial control of TNF in baboon bacteremia. *Am J Physiol* **271**:R1193–R1198.
- Reger MA, Watson GS, Frey WH, 2nd, Baker LD, Cholerton B, Keeling ML, Belongia DA, Fishel MA, Plymate SR, et al. (2006) Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype. *Neurobiol Aging* **27**:451–458.
- Reger MA, Watson GS, Green PS, Baker LD, Cholerton B, Fishel MA, Plymate SR, Cherrier MM, Schellenberg GD, Frey WH 2nd, et al. (2008) Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid-beta in memory-impaired older adults. *J Alzheimers Dis* **13**:323–331.
- Riddell DR, Zhou H, Atchison K, Warwick HK, Atkinson PJ, Jefferson J, Xu L, Aschmies S, Kirksey Y, Hu Y, et al. (2008) Impact of apolipoprotein E (ApoE) polymorphism on brain ApoE levels. *J Neurosci* **28**:11445–11453.
- Roselaar SE and Daugherty A (1998) Apolipoprotein E-deficient mice have impaired innate immune responses to *Listeria monocytogenes* in vivo. *J Lipid Res* **39**:1740–1743.
- Rowan MJ, Klyubin I, Wang Q, Hu NW, and Anwyl R (2007) Synaptic memory mechanisms: Alzheimer's disease amyloid beta-peptide-induced dysfunction. *Biochem Soc Trans* **35**:1219–1223.
- Ryan EA, O'Sullivan MJ, and Skyler JS (1985) Insulin action during pregnancy. Studies with the euglycemic clamp technique. *Diabetes* **34**:380–389.
- Ryu JK and McLarnon JG (2008) Thalidomide inhibition of perturbed vasculature and glial-derived tumor necrosis factor- α in an animal model of inflamed Alzheimer's disease brain. *Neurobiol Dis* **29**:254–266.
- Sagara M, Satoh J, Zhu XP, Takahashi K, Fukuzawa M, Muto G, Muto Y, and Toyota T (1994) Inhibition with N-acetylcysteine of enhanced production of tumor necrosis factor in streptozotocin-induced diabetic rats. *Clin Immunol Immunopathol* **71**:333–337.
- Salcedo-Tello P, Ortiz-Matamoros A, and Arias C (2011) GSK3 Function in the brain during development, neuronal plasticity, and neurodegeneration. *Int J Alzheimers Dis* **2011**:189728.
- Salloway S, Sperling R, Gilman S, Fox NC, Blennow K, Raskind M, Sabbagh M, Honig LS, Doody R, van Dyck CH, et al. (2009) A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. *Neurology* **73**:2061–2070.
- Sargin D, Friedrichs H, El-Kordi A, and Ehrenreich H (2010) Erythropoietin as neuroprotective and neuroregenerative treatment strategy: comprehensive overview of 12 years of preclinical and clinical research. *Best Pract Res Clin Anaesthesiol* **24**:573–594.
- Schiöth HB, Frey WH, Brooks SJ, and Benedict C (2012) Insulin to treat Alzheimer's disease: just follow your nose? *Expert Rev Clin Pharmacol* **5**:17–20.
- Schmidt J, Barthel K, Wrede A, Salajegheh M, Bähr M, and Dalakas MC (2008) Interrelation of inflammation and APP in sIBM: IL-1 beta induces accumulation of beta-amyloid in skeletal muscle. *Brain* **131**:1228–1240.
- Schuitmaker A, Dik MG, Veerhuis R, Scheltens P, Schoonenboom NS, Hack CE, Blankenstein MA, and Jonker C (2009) Inflammatory markers in AD and MCI patients with different biomarker profiles. *Neurobiol Aging* **30**:1885–1889.
- Seabrook TJ, Jiang L, Maier M, and Lemere CA (2006) Minocycline affects microglia activation, Abeta deposition, and behavior in APP-tg mice. *Glia* **53**:776–782.
- Serenó L, Coma M, Rodríguez M, Sánchez-Ferrer P, Sánchez MB, Gich I, Agulló JM, Pérez M, Avila J, Guardia-Laguarda C, et al. (2009) A novel GSK-3beta inhibitor reduces Alzheimer's pathology and rescues neuronal loss in vivo. *Neurobiol Dis* **35**:359–367.
- Shalaby MR, Waage A, Aarden L, and Espevik T (1989) Endotoxin tumor necrosis factor- α and interleukin-1 induce interleukin-6 production in vivo. *Clin Immunol Immunopathol* **53**:488–498.
- Shambaugh GE 3rd and Beisel WR (1967) Insulin response during tularemia in man. *Diabetes* **16**:369–376.
- Shanmugam VK, DeMaria DM, and Attinger CE (2011) Lower extremity ulcers in rheumatoid arthritis: features and response to immunosuppression. *Clin Rheumatol* **30**:849–853.
- Sharma S, Chopra K, and Kulkarni SK (2007) Effect of insulin and its combination with resveratrol or curcumin in attenuation of diabetic neuropathic pain: participation of nitric oxide and TNF- α . *Phytother Res* **21**:278–283.
- Sheng B, Wang X, Su B, Lee HG, Casadesu G, Perry G, and Zhu X (2012) Impaired mitochondrial biogenesis contributes to mitochondrial dysfunction in Alzheimer's disease. *J Neurochem* **120**:419–429.
- Shi JQ, Shen W, Chen J, Wang BR, Zhong LL, Zhu YW, Zhu HQ, Zhang QQ, Zhang YD, and Xu J (2011) Anti-TNF- α reduces amyloid plaques and tau phosphorylation and induces CD11c-positive dendritic-like cell in the APP/PS1 transgenic mouse brains. *Brain Res* **1368**:239–247.
- Simpkins JW, Gatson JW, and Wigginton JG (2009) Commentary on "a roadmap for the prevention of dementia II. Leon Thal Symposium 2008." Rationale and recommendations for first evaluating anti-Alzheimer's disease medications in acute brain injury patients. *Alzheimers Dement* **5**:143–146.
- Siqueira MF, Li J, Chehab L, Desta T, Chino T, Krothpali N, Behl Y, Alikhani M, Yang J, Braasch C, et al. (2010) Impaired wound healing in mouse models of diabetes is mediated by TNF- α dysregulation and associated with enhanced activation of forkhead box O1 (FOXO1). *Diabetologia* **53**:378–388.
- Smillie KJ and Cousin MA (2011) The role of GSK3 in presynaptic function. *Int J Alzheimers Dis* **2011**:263673.
- Smith DH, Chen XH, Iwata A, and Graham DI (2003) Amyloid beta accumulation in axons after traumatic brain injury in humans. *J Neurosurg* **98**:1072–1077.
- Soetikno V, Sari FR, Veeraveedu PT, Thandavarayan RA, Harima M, Sukumaran V, Lakshmanan AP, Suzuki K, Kawachi H, and Watanabe K (2011) Curcumin ameliorates macrophage infiltration by inhibiting NF- κ B activation and proinflammatory cytokines in streptozotocin induced-diabetic nephropathy. *Nutr Metab (Lond)* **8**:35.
- Sölling C (2011) Organ-protective and immunomodulatory effects of erythropoietin - an update on recent clinical trials. *Basic Clin Pharmacol Toxicol* **110**:113–121.
- Sommer G, Kralisch S, Lipfert J, Weise S, Krause K, Jessnitzer B, Lössner U, Blüher M, Stumvoll M, and Fasshauer M (2009) Amyloid precursor protein expression is induced by tumor necrosis factor α in 3T3-L1 adipocytes. *J Cell Biochem* **108**:1418–1422.
- Sonoda N, Katabuchi H, Tashiro H, Ohba T, Nishimura R, Minegishi T, and Okamura H (2005) Expression of variant luteinizing hormone/chorionic gonadotropin receptors and degradation of chorionic gonadotropin in human chorionic villous macrophages. *Placenta* **26**:298–307.
- Sosia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, Hyman B, Burton MA, Goldstein LE, Duong S, Tanzi RE, et al. (2010) The Alzheimer's disease-associated amyloid beta protein is an antimicrobial peptide. *PLoS One* **5**:e9505.
- Sperling RA, Jack CR Jr, and Aisen PS (2011) Testing the right target and right drug at the right stage. *Sci Transl Med* **3**:111cm33.
- Stadler J, Bentz BG, Harbrecht BG, Di Silvio M, Curran RD, Billiar TR, Hoffman RA, and Simmons RL (1992) Tumor necrosis factor- α inhibits hepatocyte mitochondrial respiration. *Ann Surg* **216**:539–546.
- Stanley LC, Mrak RE, Woody RC, Perrot LJ, Zhang S, Marshak DR, Nelson SJ, and Griffin WS (1994) Glial cytokines as neuropathogenic factors in HIV infection: pathogenic similarities to Alzheimer's disease. *J Neurobiol* **53**:231–238.
- Stellwagen D, Beattie EC, Seo JY, and Malenka RC (2005) Differential regulation of AMPA receptor and GABA receptor trafficking by tumor necrosis factor- α . *J Neurosci* **25**:3219–3228.
- Stieler JT, Bullmann T, Kohl F, Tjøen Ø, Brückner MK, Härtig W, Barnes BM, and Arendt T (2010) The physiological link between metabolic rate depression and tau phosphorylation in mammalian hibernation. *PLoS One* **6**:e14530.
- Strittmatter WJ, Saunders AM, Goedert M, Weisgraber KH, Dong LM, Jakes R, Huang DY, Pericak-Vance M, Schmechel D, and Roses AD (1994) Isoform-specific interactions of apolipoprotein E with microtubule-associated protein tau: implications for Alzheimer disease. *Proc Natl Acad Sci USA* **91**:11183–11186.
- Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, and Roses AD (1993) Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci USA* **90**:1977–1981.
- Suk K (2004) Minocycline suppresses hypoxic activation of rodent microglia in culture. *Neurosci Lett* **366**:167–171.
- Tachado SD and Schofield L (1994) Glycosylphosphatidylinositol toxin of *Trypanosoma brucei* regulates IL-1 α and TNF- α expression in macrophages by protein tyrosine kinase mediated signal transduction. *Biochem Biophys Res Commun* **205**:984–991.
- Tahara Y, Otsuka M, Fuse Y, Hirao A, and Shibata S (2011) Refeeding after fasting elicits insulin-dependent regulation of Per2 and Rev-erb α with shifts in the liver clock. *J Biol Rhythms* **26**:230–240.
- Takeuchi H, Iba M, Inoue H, Higuchi M, Takao K, Tsukita K, Karatsu Y, Iwamoto Y, Miyakawa T, Suhara T, et al. (2011) P301S mutant human tau transgenic mice manifest early symptoms of human tauopathies with dementia and altered sensorimotor gating. *PLoS One* **6**:e21050.
- Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, Stucky A, Fuino RL, Kawaguchi KR, Samoyedny AJ, Wilson RS, et al. (2012) Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *J Clin Invest* **122**:1316–1338.
- Tancredi V, D'Arcangelo G, Grassi F, Tarroni P, Palmieri G, Santoni A, and Eusebi

- F (1992) Tumor necrosis factor alters synaptic transmission in rat hippocampal slices. *Neurosci Lett* **146**:176–178.
- Tarkowski E, Andreasen N, Tarkowski A, and Blennow K (2003) Intrathecal inflammation precedes development of Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **74**:1200–1205.
- Terrano N, Monaco C, Ma D, Foxwell BM, Feldmann M, and Maze M (2010) Tumor necrosis factor- α triggers a cytokine cascade yielding postoperative cognitive decline. *Proc Natl Acad Sci USA* **107**:20518–20522.
- Thackeray JT, Radziuk J, Harper ME, Suuronen EJ, Ascsh KJ, Beanlands RS, and Dasilva JN (2011) Sympathetic nervous dysregulation in the absence of systolic left ventricular dysfunction in a rat model of insulin resistance with hyperglycemia. *Cardiovasc Diabetol* **10**:75.
- Thambisetty M, Simmons A, Velayudhan L, Hye A, Campbell J, Zhang Y, Wahlund LO, Westman E, Kinsey A, Güntert A, et al. (2010) Association of plasma clusterin concentration with severity, pathology, and progression in Alzheimer's disease. *Arch Gen Psychiatry* **67**:739–748.
- Tilley BC, Alarcón GS, Heysp SP, Trentham DE, Neuner R, Kaplan DA, Clegg DO, Leisen JC, Buckley L, Cooper SM, et al. (1995) Minocycline in rheumatoid arthritis. A 48-week, double-blind, placebo-controlled trial. MIRA Trial Group. *Ann Intern Med* **122**:81–89.
- Tissenbaum HA and Ruvkun G (1998) An insulin-like signaling pathway affects both longevity and reproduction in *Caenorhabditis elegans*. *Genetics* **148**:703–717.
- Tobinick E (2010) Perispinal etanercept: a new therapeutic paradigm in neurology. *Expert Rev Neurother* **10**:985–1002.
- Tobinick E (2011) Rapid improvement of chronic stroke deficits after perispinal etanercept: three consecutive cases. *CNS Drugs* **25**:145–155.
- Tobinick E (2012) Deciphering the physiology underlying the rapid clinical effects of perispinal etanercept in Alzheimer's disease. *Curr Alzheimer Res* **9**:99–109.
- Tobinick EL and Gross H (2008) Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration. *J Neuroinflammation* **5**:2.
- Tobinick EL, Gross H, Weinberger A, and Cohen H (2006) TNF- α modulation for treatment of Alzheimer's disease: a 6-month pilot study. *MedGenMed* **8**:25.
- Townsend M, Mehta T, and Selkoe DJ (2007) Soluble Abeta inhibits specific signal transduction cascades common to the insulin receptor pathway. *J Biol Chem* **282**:33305–33312.
- Tran HT, Sanchez L, Esparza TJ, and Brody DL (2011) Distinct temporal and anatomical distributions of amyloid-beta and tau abnormalities following controlled cortical impact in transgenic mice. *PLoS One* **6**:e25475.
- Tsai YM, Chien CF, Lin LC, and Tsai TH (2011) Curcumin and its nano-formulation: the kinetics of tissue distribution and blood-brain barrier penetration. *Int J Pharm* **416**:331–338.
- Tsampalas M, Gridelet V, Berndt S, Foidart JM, Geenen V, and Perrier d'Hauterive S (2010) Human chorionic gonadotropin: a hormone with immunological and angiogenic properties. *J Reprod Immunol* **85**:93–98.
- Tsinkalovsky O, Smaaland R, Rosenlund B, Sothorn RB, Hirt A, Steine S, Badiee A, Abrahamson JF, Eiken HG, and Laerum OD (2007) Circadian variations in clock gene expression of human bone marrow CD34+ cells. *J Biol Rhythms* **22**:140–150.
- Tükel C, Wilson RP, Nishimori JH, Pezeshki M, Chromy BA, and Bäumler AJ (2009) Responses to amyloids of microbial and host origin are mediated through toll-like receptor 2. *Cell Host Microbe* **6**:45–53.
- Tukhovskaya EA, Yukin AY, Khokhlova ON, Murashev AN, and Vitek MP (2009) COG1410, a novel apolipoprotein-E mimetic, improves functional and morphological recovery in a rat model of focal brain ischemia. *J Neurosci Res* **87**:677–682.
- Tweedie D, Sambamurti K, and Greig NH (2007) TNF- α inhibition as a treatment strategy for neurodegenerative disorders: new drug candidates and targets. *Curr Alzheimer Res* **4**:378–385.
- Uguz F, Akman C, Kucuksarac S, and Tufekci O (2009) Anti-tumor necrosis factor- α therapy is associated with less frequent mood and anxiety disorders in patients with rheumatoid arthritis. *Psychiatry Clin Neurosci* **63**:50–55.
- Uysal KT, Wiesbrock SM, Marino MW, and Hotamisligil GS (1997) Protection from obesity-induced insulin resistance in mice lacking TNF- α function. *Nature* **389**:610–614.
- Vadakkadath Meethal S and Atwood CS (2005) The role of hypothalamic-pituitary-gonadal hormones in the normal structure and functioning of the brain. *Cell Mol Life Sci* **62**:257–270.
- Valcour V, Maki P, Bacchetti P, Anastos K, Crystal H, Young M, Mack WJ, Cohen M, Golub ET, and Tien PC (2012) Insulin resistance and cognition among HIV-infected and HIV-uninfected adult women: the women's interagency HIV study. *AIDS Res Hum Retroviruses* **28**:447–453.
- Valerio A, Bertolotti P, Delbarba A, Peregó C, Dossena M, Ragni M, Spano P, Carruba MO, De Simoni MG, and Nisoli E (2011) Glycogen synthase kinase-3 inhibition reduces ischemic cerebral damage, restores impaired mitochondrial biogenesis and prevents ROS production. *J Neurochem* **116**:1148–1159.
- Valerio A, Cardile A, Cozzi V, Bracale R, Tedesco L, Pisconti A, Palomba L, Cantoni O, Clementi E, Moncada S, et al. (2006) TNF- α downregulates eNOS expression and mitochondrial biogenesis in fat and muscle of obese rodents. *J Clin Invest* **116**:2791–2798.
- Vandenbroucke K, de Haard H, Beirnaert E, Dreier T, Lauwereys M, Huyck L, Van Huyse J, Demetter P, Steidler L, Remaut E, et al. (2010) Orally administered *L. lactis* secreting an anti-TNF nanobody demonstrate efficacy in chronic colitis. *Mucosal Immunol* **3**:49–56.
- Vavra JJ, Deboer C, Dietz A, Hanka LJ, and Sokolski WT (1959) Streptozotocin, a new antibacterial antibiotic. *Antibiot Annu* **7**:230–235.
- Verhees KJ, Schols AM, Kelders MC, Op den Kamp CM, van der Velden JL, and Langen RC (2011) Glycogen synthase kinase-3beta is required for the induction of skeletal muscle atrophy. *Am J Physiol Cell Physiol* **301**:C995–C1007.
- Vitek MP, Brown CM, and Colton CA (2009) APOE genotype-specific differences in the innate immune response. *Neurobiol Aging* **30**:1350–1360.
- Vitek MP, Christensen DJ, Wilcock D, Davis J, Van Nostrand WE, Li FQ, and Colton CA (2012) APOE-mimetic peptides reduce behavioral deficits, plaques and tangles in Alzheimer's disease transgenics. *Neurodegener Dis* **10**:122–126.
- Wang AL, Yu AC, Lau LT, Lee C, Wu le M, Zhu X, and Tso MO (2005a) Minocycline inhibits LPS-induced retinal microglia activation. *Neurochem Int* **47**:152–158.
- Wang CY, Wen MS, Wang HW, Hsieh IC, Li Y, Liu PY, Lin FC, and Liao JK (2008) Increased vascular senescence and impaired endothelial progenitor cell function mediated by mutation of circadian gene Per2. *Circulation* **118**:2166–2173.
- Wang Q, Wu J, Rowan MJ, and Anwyl R (2005b) Beta-amyloid inhibition of long-term potentiation is mediated via tumor necrosis factor. *Eur J Neurosci* **22**:2827–2832.
- Wang Y, Hao Y, and Alway SE (2011) Suppression of GSK-3beta activation by M-cadherin protects myoblasts against mitochondria-associated apoptosis during myogenic differentiation. *J Cell Sci* **124**:3835–3847.
- Weiner FR, Smith PJ, Wertheimer S, and Rubin CS (1991) Regulation of gene expression by insulin and tumor necrosis factor alpha in 3T3-L1 cells. Modulation of the transcription of genes encoding acyl-CoA synthetase and stearyl-CoA desaturase-1. *J Biol Chem* **266**:23525–23528.
- Wen TS, Randall DC, and Zolman JF (1994) Protein accumulation in cerebrospinal fluid during -90 degrees head-down tilt in rabbit. *J Appl Physiol* **77**:1081–1086.
- Wen Y, Yang S, Liu R, Brun-Zinkernagel AM, Koulen P, and Simpkins JW (2004a) Transient cerebral ischemia induces aberrant neuronal cell cycle re-entry and Alzheimer's disease-like tauopathy in female rats. *J Biol Chem* **279**:22684–22692.
- Wen Y, Yang S, Liu R, and Simpkins JW (2004b) Transient cerebral ischemia induces site-specific hyperphosphorylation of tau protein. *Brain Res* **1022**:30–38.
- Westermann D, Van Linthout S, Dhayat S, Dhayat N, Schmidt A, Noutsias M, Song XY, Spillmann F, Riad A, Schultheiss HP, et al. (2007) Tumor necrosis factor- α antagonism protects from myocardial inflammation and fibrosis in experimental diabetic cardiomyopathy. *Basic Res Cardiol* **102**:500–507.
- Wilson AC, Clemente L, Liu T, Bowen RL, Meethal SV, and Atwood CS (2008) Reproductive hormones regulate the selective permeability of the blood-brain barrier. *Biochim Biophys Acta* **1782**:401–407.
- Wu SR, Li CF, Hung LY, Huang AM, Tseng JT, Tso JH, and Wang JM (2011) CCAAT/enhancer-binding protein delta mediates tumor necrosis factor alpha-induced Aurora kinase C transcription and promotes genomic instability. *J Biol Chem* **286**:28662–28670.
- Xu Y, Tian Y, Wei HJ, Chen J, Dong JF, Zacharek A, and Zhang JN (2011) Erythropoietin increases circulating endothelial progenitor cells and reduces the formation and progression of cerebral aneurysm in rats. *Neuroscience* **181**:292–299.
- Yamakawa I, Kojima H, Terashima T, Katagi M, Oi J, Urabe H, Sanada M, Kawai H, Chan L, Yasuda H, et al. (2011) Inactivation of TNF alpha ameliorates diabetic neuropathy in mice. *Am J Physiol Endocrinol Metab* **301**:E844–E852.
- Yamamoto M, Kiyota T, Horiba M, Buescher JL, Walsh SM, Gendelman HE, and Ikezu T (2007) Interferon-gamma and tumor necrosis factor- α regulate amyloid-beta plaque deposition and beta-secretase expression in Swedish mutant APP transgenic mice. *Am J Pathol* **170**:680–692.
- Yang Y and Herrup K (2007) Cell division in the CNS: protective response or lethal event in post-mitotic neurons? *Biochim Biophys Acta* **1772**:457–466.
- Yazdani-Biuki B, Stelzl H, Brezinschek HP, Hermann J, Mueller T, Krippel P, Graninger W, and Wascher TC (2004) Improvement of insulin sensitivity in insulin resistant subjects during prolonged treatment with the anti-TNF- α antibody infliximab. *Eur J Clin Invest* **34**:641–642.
- Yokota S (2003) Influenza-associated encephalopathy—pathophysiology and disease mechanisms. *Nippon Rinsho* **61**:1953–1958.
- Young-Collier KJ, McArdle M, and Bennett JP (2012) The dying of the light: mitochondrial failure in Alzheimer's disease. *J Alzheimers Dis* **28**:771–781.
- Zauli G, Toffoli B, di Iasio MG, Celeghini C, Fabris B, and Secchiero P (2010) Treatment with recombinant tumor necrosis factor-related apoptosis-inducing ligand alleviates the severity of streptozotocin-induced diabetes. *Diabetes* **59**:1261–1265.
- Zhang Q, Raouf M, Chen Y, Sumi Y, Sursal T, Junger W, Brohi K, Itagaki K, and Hauser CJ (2010) Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature* **464**:104–107.
- Zhou QH, Boado RJ, Hui EK, Lu JZ, and Pardridge WM (2011) Brain-penetrating tumor necrosis factor decoy receptor in the mouse. *Drug Metab Dispos* **39**:71–76.
- Ziegler SG and Thornton JE (2010) Low luteinizing hormone enhances spatial memory and has protective effects on memory loss in rats. *Horm Behav* **58**:705–713.
- Zotova E, Nicoll JA, Kalaria R, Holmes C, and Boche D (2010) Inflammation in Alzheimer's disease: relevance to pathogenesis and therapy. *Alzheimers Res Ther* **2**:1.