

## Targeting tumor necrosis factor- $\alpha$ in hypoxia and synaptic signaling

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### Abstract

Tumor necrosis factor (TNF)- $\alpha$  is a pro-inflammatory cytokine, which is synthesised and released in the brain by astrocytes, microglia and neurons in response to numerous internal and external stimuli. It is involved in many physiological and pathophysiological processes such as gene transcription, cell proliferation, apoptosis, synaptic signalling and neuroprotection. The complex actions of TNF- $\alpha$  in the brain are under intense investigation. TNF- $\alpha$  has the ability to induce selective necrosis of some cells whilst sparing others and this has led researchers to discover multiple activated signalling cascades. In many human diseases including acute stroke and inflammation and those involving hypoxia, levels of TNF- $\alpha$  are increased throughout different brain regions. TNF- $\alpha$  signalling may also have several positive and negative effects on neuronal function including glutamatergic synaptic transmission and plasticity. Exogenous TNF- $\alpha$  may also exacerbate the neuronal response to hypoxia. This review will summarise the actions of TNF- $\alpha$  in the central nervous system on synaptic signalling and its effects during hypoxia.

**Key words:** TNF- $\alpha$ ; hypoxia; prolyl hydroxylase; hippocampus; synaptic transmission; synaptic plasticity; inflammation

### Introduction

Tumor necrosis factor (TNF)- $\alpha$  is a pro-inflammatory cytokine which was initially described as a necrotic factor in peripheral inflammation which induced cell death in tumour cell lines *in vitro* and transplanted tumours *in vivo* [1]. In the brain it is synthesised and released by astrocytes [2], microglia [3], and neurons [4, 5]. It is constitutively expressed as its non-active larger trans-membrane form (26 kDa protein), which is cleaved at its extracellular domain by TNF- $\alpha$  converting enzyme (TACE) to produce a 17 kDa active protein, by a process known as 'ectodomain shedding' [6]. The varied and complex functions

of TNF- $\alpha$  are currently under intense investigation. To date TNF- $\alpha$  has been shown to be involved in a multiplicity of physiological processes such as cell proliferation and differentiation [7, 8], gene transcription [9, 10], and up-regulation of neuroprotective mediators [11, 12]. It is TNF- $\alpha$ 's ability to induce selective necrosis of some cells whilst sparing others that has led researchers to discover multiple activated signalling cascades.

There is much evidence to date that TNF- $\alpha$  and TNF receptor (TNFR) signalling is increased in many neurological disorders including Alzheimer's disease, Parkinson's disease, ischemia, multiple sclerosis and traumatic brain injury [13-17] to name but a few. It is also now widely accepted that centrally expressed TNF- $\alpha$  can regulate synaptic signalling and synaptic plasticity and induce structural changes at the synaptic level [18, 19]. This review will focus on the actions of TNF- $\alpha$ , through its central receptors in the central nervous system, on synaptic signalling and plasticity and the effects of TNF- $\alpha$  during hypoxia.

### TNF- $\alpha$ receptor expression and signal transduction in the CNS

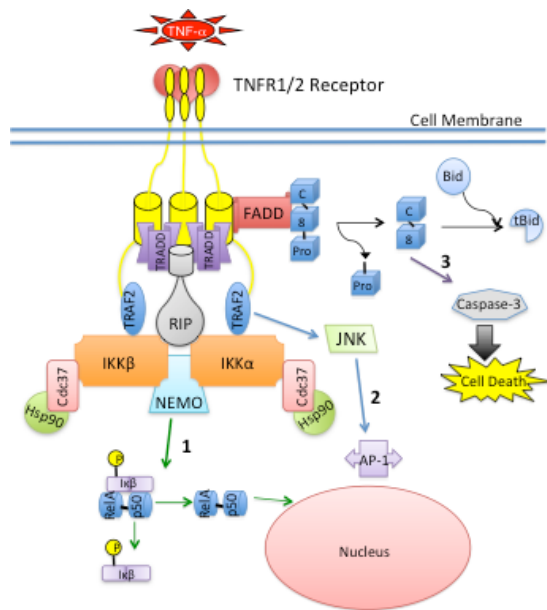
TNF- $\alpha$  surface receptors are found on both neuronal [20, 21] and glial cell population [22], along with endothelial cells of the cerebral vasculature [23]. Two distinct TNF- $\alpha$  receptors have been identified, the low affinity TNFR1 (p55) and the high affinity TNFR2 (p75) receptor [24]. Binding of homotrimeric TNF- $\alpha$  to either receptor can activate three major signaling cascades [25]. First, there can be an interaction of the ligand-bound TNF receptor with the TNF receptor-associated death domain (TRADD), initiating the apoptotic-signaling cascade. This causes the recruitment of fas and its internalization and subsequent activation of caspase-8 [26]. Second, TNF- $\alpha$  can activate the nuclear factor kappa B (NF $\kappa$ B) signaling pathway where it translocates to the nucleus and regulates gene transcription. The activation of NF $\kappa$ B signaling by the TNF receptor can promote cell survival signal cascades. It seems that the rate and persistence of NF $\kappa$ B activation differ depending on receptor subtype activated, which may account for the difference in their overall response [27]. Third, TNF- $\alpha$  can activate the JNK signaling pathway

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resulting in the enhanced activity of several transcription factors such as AP-1. These signalling cascades are not mutually exclusive to the individual receptors [28]. Most cell types express both TNFR1 and TNFR2 receptors and thus the overlap in their signalling cascades adds to the complexity of the overall effect of TNF- $\alpha$ . Finally it has been postulated that it is the ratio of TNFR1: TNFR2 receptor expression that may govern the overall outcome of TNF- $\alpha$  action. Figure 1 shows a schematic cartoon of the signalling events triggered by activation of TNFR1 and TNFR2 in the brain.



**Figure 1**

#### *TNF- $\alpha$ signalling pathways*

Binding of TNF- $\alpha$  to TNFR1 or TNFR2 can activate three major signalling cascades (labelled 1, 2 and 3). Activation of TNFR1 results in the configuration of TRADD (TNFR-associated death domain) and FADD (Fas-associated death domain). TRADD complex recruits the adapter protein TRAF-2 (TNFR-associated factor 2), whereas FADD stimulates the caspase cascade. Known downstream signalling molecules that interact with TRAF-2 include NIK (NF- $\kappa$ B-inducing kinase), RIP (receptor-interacting protein) and ASK1 (apoptosis signal-regulating kinase 1) and these are capable of channelling signals towards cell death and inflammation. Binding of TNF- $\alpha$  to TNFR2 recruits the adapter protein TRAF-2, which directly activates the inflammatory cascade via the generation of NF- $\kappa$ B or p38 MAPK (mitogen-activated protein kinase) and activates caspase-mediated cell death through recruitment of FADD and RIP.

#### **TNF- $\alpha$ and synaptic signalling**

There is now accumulated evidence that TNFR signalling is correlated with glutamatergic synaptic transmission and plasticity [29]. Long-term treatment with TNF- $\alpha$  was shown to enhance calcium currents and reduce N-methyl-D-aspartate (NMDA)-induced currents by a mechanism

involving activation of NF- $\kappa$ B [30]. TNFR receptor activation increases  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA) trafficking to the membrane surface of neurons while decreasing GABA $_A$  receptor surface expression [31]. These TNFR signalling effects were mediated by increases in the amplitude and frequency of mEPSCs and decreases in the amplitude of mIPSCs [29, 32]. Direct inhibition of endogenous TNF- $\alpha$  could also bring about these effects on AMPARs [29, 33]. Most recently, He et al., [34] have shown that deletion of TNFR1 plays a critical role in decreasing AMPAR clustering, which was not restored by exposure to exogenous TNF- $\alpha$  suggesting a role for TNFR1 signaling in the maintenance of the basal AMPAR membrane stability. No role for TNFR2 was demonstrated in these experiments. The authors conclude that experimental designs targeting TNFR1 but not TNFR2 may help to reduce excitotoxicity in neurons. TNF- $\alpha$  can also directly modulate Ca $^{++}$  dynamics and Ca $^{++}$  fluxes into neurones [35]. Santello et al., [36], has recently demonstrate that gliotransmission and its synaptic effects are controlled not only by astrocyte intracellular calcium elevations but also by permissive/homeostatic factors like TNF- $\alpha$ .

#### **TNF- $\alpha$ and synaptic plasticity**

In the early 90s exogenous application of TNF- $\alpha$  was shown to have inhibitory effects on synaptic plasticity and long-term potentiation (LTP), an electrophysiological correlate of learning and memory [37, 38]. Later it was shown that the JNK and p38 MAP kinase played an important role in this inhibitory effect on LTP [39, 40]. These mechanisms may be similar for the effects of other pro-inflammatory cytokines such as IL-1 $\beta$  on LTP [41, 42]. It would seem that p38 MAPK plays a role in early LTP but not late LTP [39]. The inhibitory effects of TNF on LTP were also augmented by nicotine application [43], whilst  $\alpha$ -methyl-4-carboxyphenylglycine (MCPG), 2-methyl-6-(phenylethynyl)pyridine (MPEP; both antagonists for the metabotropic glutamate receptor) and ryanodine, reversed the inhibitory effect of TNF- $\alpha$  on LTP [44]. Interestingly knock out mice for TNFR1 show full LTP, highlighting potential differences in basal activity of TNF- $\alpha$  and excessive production of TNF- $\alpha$  [31].

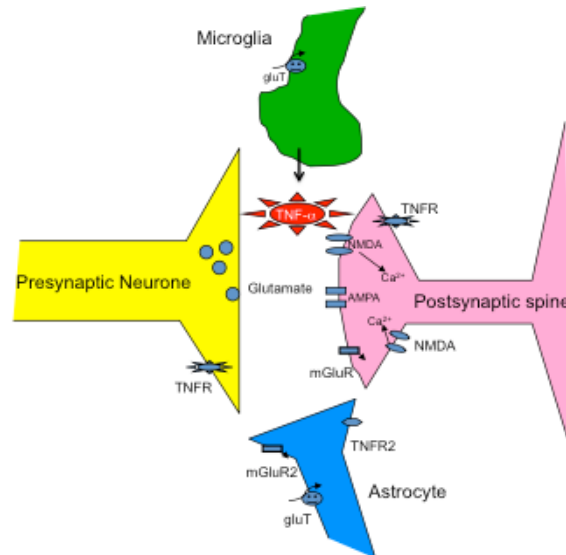
TNF- $\alpha$  signaling has also been shown to have a role in long-term depression (LTD), another electrophysiological process purported to provide insight into memory consolidation. Mice deficient for TNF- $\alpha$  receptors (TNFR-KO mice) display no LTD [45]. Its modulation of synaptic plasticity (LTP and LTD) is predominantly as a result of the direct neuronal-glial cross talk. During synaptic transmission glutamate-mediated activation of glial metabotropic glutamate receptors (mGluRs) may stimulate the release of TNF- $\alpha$  into the

synapse [46]. TNF- $\alpha$  can then diffuse and bind to its receptors found on the neuronal plasma membranes and initiate signalling cascades involved in increased synthesis and trafficking of AMPA receptors to the post synaptic density, thus enhancing synaptic efficacy [29]. Indeed, this study by Beattie, also demonstrated that by removing TNF- $\alpha$  mediated signalling, using soluble TNFR1 decoy receptor, a reduction in AMPAR surface expression on hippocampal neuronal membranes occurred [29]. These findings highlight the important contribution of the inflammatory mediator to the maintenance and modulation of hippocampal excitatory synapses (a process known as synaptic scaling). Thus under normal physiological and pathophysiological levels TNF- $\alpha$  plays an important role in the regulation of synaptic plasticity and in the consolidation of memory within the hippocampus [32, 39, 45].

### TNF- $\alpha$ and hypoxia in the CNS

When faced with low blood oxygen levels, hypoxia, humans reflexly engage a number of physiological changes as well as cellular intrinsic homeostatic mechanisms [47]. To date most research has concentrated on the cellular adaptation that requires long-term adaptive changes including gene expression changes, which involve transcription factors [48]. Another problem associated with hypoxia is the acute and chronic occurrence of inflammation in the affected region with the release of pro inflammatory cytokines such as TNF- $\alpha$ . TNF- $\alpha$  has been shown to interact with adenosine in its effects during hypoxia. Very little is known about this interaction [49, 50]. Hypoxia induces oxidative stress in the brain [51, 52] and is associated with increased levels of pro-inflammatory cytokines, such as TNF- $\alpha$  in pig [53], in humans [54] and in mice [55]. Indeed, the levels of TNF- $\alpha$  may remain elevated in the affected brain tissue for at least 24 h after an ischemic insult [16, 56] and TNF- $\alpha$  itself causes oxidative stress in the brain [57].

Past studies have shown that the excess glutamate produced by excitatory amino-acid transporter (EAAT) inactivation may be a key component in the contribution of TNF- $\alpha$  to cerebral hypoxia and ischemia. This excess glutamate remains in the extracellular space leading to glutamate-induced excitotoxicity due to EAAT dysfunction during ischemia. TNF- $\alpha$  signaling through TNFR1, caspase and ceramide, can be neurotoxic to cells and induce apoptosis while TNF- $\alpha$  signaling through TNFR2 and gene transcription pathways has neuro-protective effects in neurones and glia. Most recently it has been shown that TNF- $\alpha$  is neuro-protective against hypoxia-induced hyperexcitability in hippocampal neurons [58].



**Figure 2**

### *TNF- $\alpha$ and synaptic signalling*

TNF- $\alpha$  can directly modulate neuronal function by activation of the TNFRs expressed on the pre- and post-synaptic neuronal membranes. TNF- $\alpha$  can modulate astrocyte function via activation of predominantly TNFR2. Glutamate can also indirectly enhance neuronal toxicity by stimulating TNF- $\alpha$  release from microglia. Activation of TNFR1 can lead to apoptosis while TNFR2 activation can lead to neuroprotection against glutamate induced excitotoxicity.

Some of the first evidence showing a link between TNF- $\alpha$  and hypoxia inducible factor, a key regulator in the transcriptional response to hypoxia, came from the laboratory of Zhou et al., where they showed that TNF- $\alpha$  released from activated macrophages could stabilize HIF-1 $\alpha$  in resting tubular LLC-PK1 cells [59]. Also Jung et al., [60], described a novel mechanism of HIF-1 $\alpha$  up-regulation and they identified HIF-1 $\alpha$  as a unique component of the NF-kappa B-mediated inflammatory/survival response. More recently Goel et al., [61] suggest that TNF- $\alpha$  and HSP-70 together enhance the decrease in pro-apoptotic protein levels and the increase in anti-apoptotic protein levels in the event of neuronal hypoxia through ERK1/2 signal transduction. It has also been shown that that apoptosis of cortical neurons after oxygen-glucose deprivation (OGD) is mediated by TNF- $\alpha$  /TNF- $\alpha$  receptor 1 [62]. The novel cytokine, tumor necrosis factor-like weak inducer of apoptosis (TWEAK) may be a potential prophylactic strategy to protect the brain from the devastating effects of an ischemic injury. Also the cytokine tumor necrosis factor-like weak inducer of apoptosis and its receptor fibroblast growth factor-inducible 14 have a neuroprotective effect in the central nervous system [63].

Our laboratories have recently shown that the recovery of hippocampal neurons from two hours hypoxia can be significantly impaired by addition of pathophysiological levels of TNF- $\alpha$  [64]. This

effect was reversed by prior application of a p38MAPK inhibitor. A novel role for prolyl hydroxylases (which regulate HIF1- $\alpha$  stability in neurons) and TNF- $\alpha$  during hypoxia may also be emerging. Our laboratories have recently shown that synaptic plasticity in the dentate gyrus is significantly enhanced post hypoxia and in the presence of exogenous TNF- $\alpha$  [65, 66]. Together, all of these studies highlight the vast detrimental effects of TNF- $\alpha$  on both glial and neuronal functioning during cerebral hypoxia and ischemia.

### Concluding remarks

It is now accepted that the role of TNF- $\alpha$  as a central neuro-inflammatory mediator also extends to complex physiological processes in the CNS. Its many signalling cascades give rise to multiple effects on synaptic transmission and plasticity. TNF- $\alpha$  also plays a major role in hypoxic and ischemic events in the brain. Our understanding of the role of this pro-inflammatory agent in these effects will undoubtedly give rise to new therapeutic targets.

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