Applied Network Science

RESEARCH Open Access

Computational modelling of TNFα related pathways regulated by neuroinflammation, oxidative stress and insulin resistance in neurodegeneration

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Abstract

Computational and mathematical modelling towards understanding the structure and dynamics of biological systems has significantly impacted on translational neuroscience to face novel approaches toward neurological disorders such as Alzheimer's (AD) and Parkinson's disease (PD). In this study, a computational model of AD and PD have been modelled using biochemical systems theory, and shows how Tumour Necrosis Factor alpha (TNF훼) regulated neuroinflammation, oxidative stress and insulin pathways can dysregulate its downstream signalling cascade that lead to neurodegeneration observed in AD and PD. The experimental data for initial conditions for this model and validation of the model was based on data reported in literature. In simulations, elevations in the aggregations of major proteins involved in the pathology of AD and PD including amyloid beta, alpha synuclein, tau have been modelled. Abnormal aggregation of these proteins and hyperphosphorylation of tau were observed in the model. This aggregation may lead to developing Lewy bodies, fibrils, plaques and tangles inside neurons that trigger apoptosis. An increase in the concentrations of TNF훼 and glutamate during diseased conditions was noted in the model. Accumulation of these proteins may be related to the feedback mechanism of TNF훼 that initiates its own release and the production of excess glutamate. This could lead to the prolonged activation of microglia that result in death of surrounding neurons. With the elevation in reactive oxygen species, oxidative stress also increased. Simulations suggest insulin may be an important factor identifying neurodegeneration in AD and PD, through its action along with the neuroinflammation and oxidative stress. Low insulin level was noticed in the diseased condition due to abnormal protein aggregation that leads to TNFα release. Given the role towards better design of real experiments, accumulation of oligomers of mutated proteins in AD and PD activating microglia and secreting TNFα along with other cytokines map to oxidative stress that led to cell death.

Keywords: Tumor necrosis factor alpha, Insulin, Parkinson's disease, Alzheimer's disease, Systems theory, Mathematical modelling, Inflammation, Oxidative stress

Introduction

Alzheimer's disease (AD) is a major neurodegenerative disorder often related to the deposition of amyloid β-peptide (Aβ) plaques in brain tissue followed by formation of neurofibrillary tangles (Murphy and Levine 2010) and is associated to symptoms such as memory loss, alterations in mood and behavior and have been associated with, dementia, disorientation and aphasia (Jahn 2013). Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder that causes death of dopaminergic neurons in substantia nigra pars compacta of the midbrain, which leads to the decline in the synthesis of dopamine (Mhyre et al. 2012). It is also characterised by a large number of motor and non-motor features and by the increase in incidence above the age of 65 (Mahlknecht et al. 2015). The clinical manifestations of PD include resting tremor, muscular rigidity, bradykinesia, depression and postural instability (DeMaagd and Philip 2015). According to the Alzheimer's Association, National Institutes of Health in the United States of America spends $480 million on Alzheimer's research compared to $3 billion on HIV/AIDS, $4 billion on heart disease and $6 billion on cancer. PD affects 1–2 per 1000 of the population with its prevalence increasing with age and affecting about 1% of the population above 60 years (Tysnes and Storstein 2017). Therefore, discovery and characterization of accurate biomarkers play a crucial role in disease prediction (Padmanabhan et al. 2017). Both, genetic and environmental factors, have been identified related to the risks of developing AD (Killin et al. 2016). If the condition can be detected earlier, effective treatment can help manage the condition although, often, fewer symptoms manifest in the early stages resulting in late detection of the disease. The biomarkers till date change with the factors and illness, and it may not be expressed all the time. One of the main medications given for PD patients is L-Dopa (Hardebo and Owman 1980). Although, several experimental models to analyse the disease pathology have been developed, there are aspects regarding the pathological cascade of both sporadic and familial conditions (Golde et al. 2013; Ferreira et al. 2015) that need to be addressed. A reason behind this is the limitations in conducting in vitro and in vivo experiments with neurons (Polikov et al. 2007) and the complexity in neuronal circuits. For example, in the case of AD, it is difficult to extract β amyloid aggregates from neural specimens, and previous reports indicate aggregates in saline cause toxicity in vitro (Esparza et al. 2016; Giorgetti et al. 2018). Although there is evidence that amyloid β oligomers contribute chronic neurological manifestations, they are difficult to be detected by conventional staining techniques (Ferreira et al. 2015).

There are some drugs available to manage the symptoms, despite decades of research, no treatment has been reported to completely halt the disease conditions yet (Padmanabhan et al. 2017). Since the disease mechanisms are poorly understood, especially in case of major proteins such as alpha synuclein (αS), amyloid β and tau that form fibrils, plaques and tangles, it is difficult to turn them off and patients are diagnosed late or remain undiagnosed (Bendor et al. 2013; Razzokov et al. 2019). Studies have also suggested the accumulation of Aβ and αS in the brain during the natural process of aging (Li et al. 2004). As these aggregated proteins lead to signal cross-talk within the brain, it may be associated to further signalling cascades which initiates onset of the disease. This includes several abnormal cell damage events such as mitochondrial dysfunction, oxidative stress, hyperphosphorylation of tau, increased neuro-inflammatory responses, decreased neuroplasticity and neurogenesis, neurodegeneration etc. (de JR de Paula

et al. 2009). Recent studies have shown that during neuroinflammation, the release of TNFα by activated astrocytes and microglia was linked to AD and PD (Reddy and Seth n.d. ; Olmos and Lladó 2014).

Inflammation in the brain may be promoted by invasion of pathogens, spinal cord injury, aggregation of misfolded proteins, tangles, plaques. The cellular insults activate microglia and initiate the production of proinflammatory cytokines to protect neurons from tissue damage initially, which results in neurodegeneration (Amor et al. 2010). Tumour necrosis factor alpha (TNF훼), a major proinflammatory cytokine, has been known to have an important role in neuroinflammation and glutamate mediated excitotoxicity related to AD and PD (A Frankola et al. 2011; Olmos and Lladó 2014). It has been reported that TNFα along with surface receptors, are present in healthy brain at low levels, and high levels in diseased states (Santello and Volterra 2012). Under normal physiological conditions, the production of excess TNFα is controlled by inhibiting activation of microglia (Wang et al. 2015). During inflammation, astrocytes and microglia become activated through initiation of proinflammatory triggers and cytokines release due to T cells infiltration (Liberman et al. 2019). Aβ and αS have been reported as key proteins that trigger neuroinflammation in AD and PD respectively (Tweedie et al. 2012). Amyloid plaques have been known to cause neurodegeneration due to the toxic effect of Aβ (Pasinetti and Hiller-Sturmhöfel 2008). Hyperphosphorylation of tau forms neurofibrillary tangles that again leads to intracellular lesions in the brain (de JR de Paula et al. 2009). In vitro and in vivo studies have shown that mutations in genes code of amyloid precursor protein, presenilin 1 and 2 trigger plaque formation (Żekanowski et al. 2003). In earlier studies, the involvement and presence of TNFα around Aβ plaques have been reported in the post-mortem brain tissue of both transgenic AD mice and AD conditions (Chang et al. 2017). A study had reported the role of neuroinflammation and TNFα signalling in the early stages of AD and its role in neurodegeneration through accumulation of plaques, neurofibrillary tangles and elevations of misfolded or mutated proteins/genes involved (Montgomery and Bowers 2012). Experiments on both animal and human PD brain tissues suggested that abnormal levels of TNFα released by high microglial activation can lead to dopaminergic cell death (Yiannopoulou and Papageorgiou 2013). Elevation in accumulation of αS aggregates activates microglia in turn increasing the production and release of excess TNFα (Zhang et al. 2018). Both Aβ plaques and αS aggregation can lead to elevated levels of TNFα that eventually results in the progression of AD or PD pathology (Decourt et al. 2016). Cellular and molecular changes implicate increased TNFα levels by microglial activation in both AD and PD, which suggests a commonness in TNFα signalling pathway in the progression of both these diseases (A Frankola et al. 2011). Several studies have indicated changes in oxidative stress due to increased level of reactive oxygen species (ROS) which was induced by TNFα signalling in AD and PD (Fischer and Maier 2015). In both AD and PD conditions, accumulation of abnormal αS and Aβ lead to oxidative stress that trigger the apoptotic pathway (Singh et al. 2019).

Brain's insulin sensitivity has been studied (Blázquez et al. 2014) and insulin has been known to regulate cellular mechanisms inside the brain (Plum et al. 2005). Insulin has also been documented to regulate various brain functions such as neuroprotection, synaptic plasticity, memory, and reward recognition (Ferrario et al. 2018). The cellular links between insulin resistance and neurodegeneration in PD related pathological mechanisms have been previously discussed (Athauda and Foltynie 2016). Impaired insulin signalling pathway has also been identified as a critical pathological factor

contributing to the development of AD (Hölscher 2014). Impaired insulin signalling has been known to be associated to the formation of plaques, tangles, increased oxidative stress, and important factors facilitating neurodegeneration in AD (Rad et al. 2018). Experimental models have shown the critical role of insulin signalling pathway in degradation of Aβ and αS and blocking them led to formation of toxic fibrils and plaques (Sharma and Singh 2016). Insulin signalling and neuroinflammation may be co-related, with an imbalance possibly inducing an elevation in inflammatory cytokines including TNFα as observed during AD and PD (Yang et al. 2018). There is a need to re-analyze the roles and relationships of TNFα signalling, activation of glial cells, oxidative stress, insulin resistance and accumulation of misfolded/mutated protein aggregates that are linked to each other, share common genes and possibly signalling pathways, that may lead to neurodegeneration in both AD and PD pathology.

Modelling disease related signalling pathways in silico helps in understanding the experimentally-relevant relationships between individual proteins, interactions and related perturbations which are crucial for analysing disease mechanisms and for mapping appropriate therapeutic targets (Vidal et al. 2011; Hao et al. 2018). Modelling complex biological pathway networks including their cellular and molecular components, and interactions (Ji et al. 2017) can help connect critical factors statistically relevant as common signaling mechanisms or phentotypic functions to both disorders. Developing computational models can aid reproducing disease pathways and predicting dynamical behaviours essential for approprite protocol design and experimental testing and to map clinical symptoms to molecular processes going through cellular and circuit functions (Conradi et al. 2007; Bartocci and Lió 2016). Using biochemical systems theory (BST), sub-cellular reactions and biochemical pathways were modeled using ordinary differential equations (ODE) for reconstructing signalling dynamics in this study (Savageau et al. 1987). All biochemical reactions involved in disease-related signalling pathways were expressed mathematically using ODE and rate equations were computed using computational tools (Bartocci and Lió 2016).

The objective of this modeling exercise was to map major genes or proteins involved in disease mechanism, the reactions affected by the mutation of these genes and the difference in reactions when compared with healthy controls, action ofpotential drugs. In literature, BST models on oxidative stress and inflammation in insulin resistance were already available for PD condition (Braatz and Coleman 2015). These models explore some of the important pathways involved in PD and the treatment options. Most of the initial conditions for the model parameters were assigned as relative values rather than real data. With the need to model crosstalk and critical networks relevant to neurodegeneration identified by more recent studies, we have incorporated the crosstalk between insulin resistance, oxidative stress and neuroinflammation related to TNFα signalling in normal, AD and PD conditions (Fallahi-Sichani et al. 2011; Sasidharakurup et al. 2020; Su and Wu 2020). The parameteric values relating to biological states and initial conditions for this model were manually extracted from literature on disease models. In a previous study, we had modelled the role of TNFα mediated glutamate excitotoxicity and neuroinflammation (Sasidharakurup et al. 2020) and the variations in TNFα levels during both healthy and diseased conditions were analyzed. Some autocrine loops co-involved in the activation of TNFα were also modeled to study how TNF훼 stimulates its own release. To extend the relationships between AD and PD, this present study focuses on developing a model of TNFα related pathways regulated

by neuroinflammation, oxidative stress and insulin resistance during neurodegeneration. In addition, few of the crucial feedback loops involved in TNFα signalling and their emergent properties maintaining the disease condition needed to be incorporated. Aimed towards building a tool for designing experimental interventions and connecting to clinically relevant biomarkers, common cellular components found in both AD and PD conditions, that trigger TNFα signalling such as Aβ, αS, tau phosphorylation, calcium, glutamate etc. were modelled in this paper.

Methods

Major pathways involved in TNFα signalling regulated by inflammation, oxidative stress and insulin resistance that leads to neuronal death were modelled in this paper using biochemical systems theory. Pathways were mathematically reconstructed and simulations were done by using CellDesigner (Funahashi et al. 2006). All reactions were modelled as networks with genes, proteins and other cellular components represented as nodes in the network. Reactions were inter-connected using corresponding kinetic formulae. In this reconstruction, all reactions were mathematically represented using ODE, and initial concentration values and rate constant values were assigned.

The law of mass action and Michaelis-Menten (MM) kinetics were used to approximate reaction values and to model enzyme reactions (see Eq. (1) and Eq. (2)).

Michaelis-Menten kinetics

Enzyme-involved reactions were mathematically expressed using MM kinetics.

$$v = \frac{d[p]}{dt} = \frac{v_{max}[s]}{k_m + [s]} \tag{1}$$

Where, Vmax was the maximum rate achieved by the system, at saturating substrate concentration in relation of reaction rate v to [s], where [s] was the concentration of a substrate S. K_m was Michealis constant was the rate constant and the rate constant K_m (Michaelis constant) was equal to [s] when v is half of V_{max}.

Generalized mass action (GMA) kinetics

Each reaction was approximated using the power law equation, represented as a system of ODE (Tucker et al. 2007):

$$\dot{x}_i = \sum_{k=1}^{n+m}\left[\pm\gamma_{kp}\prod_{j=1}^{n}X_j^{f_{ijk}}\right] \tag{2}$$

Where i = (1, …, d). Each variable x_i represented the concentration of a reactant, and $\dot{x}_i$ denoted the time derivative of x_i. In the model, the parameters γ_{kp} were rate constants, whereas the parameters f_{ijk} were kinetic orders.

The concentrations parameters in the MM approximation and in ODEs were estimated from experimental data that have quantified by common molecular biology techniques including ELISA, western blotting, radioenzymatic assay, HPLC, mass spectrometry and the rate parameters were obtained from previous modelling or from in vitro studies on normal and diseased tissues. Table 1, reports the known critical proteins in the model of AD pathway, their concentration values, corresponding

Table 1 Experimental data sources for concentrations and related literature in AD. The concentrations parameters of individual genes involved in the cellular pathways of Alzheimer's disease were adapted from experimental studies listed here.

Protein/ gene	Experiment	Region	Model	Concentration		References
				Control	Diseased	
TNFα	EIA assay	CSF	Humans	22.3 + 9.5 pg/ml	96.3 + 9.1 pg/ml	(Mogi et al. 1994)
Tau	Sandwich ELISA	CSF	Human (in vitro)	288 ± 160 pg/mL	728 ± 432 pg/mL	(Kester et al. 2009)
Aβ42	Sandwich ELISA	CSF	Human (in vitro)	845 ± 222 pg/mL	459 ± 170 pg/mL	(Kester et al. 2009)
Calcium	Inductively Coupled Plasma Mass Spectrometry (ICP MS)	Serum	Human (in vitro)	7.2 ± 2.6 μg/L	8.1 ± 2.1 μg/L	(Paglia et al. 2016)
APP	SDS PAGE followed by western blotting and densitometric scanning	Hippocampus	Human (in vitro)	0.98 ± 0.32 per 5.0 μg protein	1.92 ± 0.57 per 5.0 μg protein	(Davidsson et al. 2001)
αS	Newly developed bead based xMAP technology assay	CSF	Human (in vitro)	67 ng/L	94 ng/L	(Hansson et al. 2014)
IL-6	Commercial plate-based ELISA	Plasma	Human (in vitro)	1.622 ± 0.806 pg/mL	2.343 ± 1.379 pg/mL	(Wu et al. 2015)
NOS	Assayed by measuring conversion of arginine to citrulline	Microvessels	Human (in vitro)	10.0 ± 2.4 nmol/min/mg	44.7 ± 5.5 nmol/min/mg	(Dorheim et al. 1994)
GSK-3	EIA assay	Post Synaptosomal supernatant	Human (in vitro)	156.41 ± 12.07 pmol phosphate incorporated/mg protein/min	160.78 ± 29.6 pmol phosphate incorporated /mg protein/min	(Pei et al. 1997)

experiments, the experimental model and related literature reference. For biologically valid reconstructions, the model included the concentration values of important proteins including TNFα (Mogi et al. 1994), tau (Kester et al. 2009), Aβ (Kester et al. 2009), calcium (Paglia et al. 2016), APP (Davidsson et al. 2001), αS (Hansson et al. 2014), IL-6 (Wu et al. 2015), NOS (Dorheim et al. 1994), GSK-3 (Pei et al. 1997) both in control and AD conditions.

Experiment-derived values (see Table 2) for concentrations of TNFα (Mogi et al. 1994), glutamate (Iwasaki et al. 1992), calcium (Putney and Tomita 2011), TNFR1 (de JR de Paula et al. 2009), αS (Oczkowska et al. 2014), ROS (Tretter and Dam-Vizi 2004), IL-1β (Hu et al. 2015) and tau (Blennow et al. 1995) in control and PD conditions were incorporated into the model.

Using this literature data, the biochemical networks in AD and PD have been modelled from simple reactions to generate complex networks made from proteins and other biomolecules as in experimental observations. For example, in the case of TNFα signalling, the emergent properties of the system (see Fig. 1) were related to three vicious circles (Olmos and Lladó 2014).. As reported earlier, initial concentration values for the model were extracted from available experimental data either from studies conducted on neurons in the post-mortem brain of patients or from experimental animal models. For example, initial concentration values for TNFα in case of normal and diseased conditions were taken from a study by Mogi et al. (1994) where the elevated

Table 2 Experimental data sources for concentrations and related literature in PD. The values for modeling the concentrations of individual genes involved in the biochemical pathways of PD were adapted from experimental data listed as references

Protein/ gene name	Experiment	Region	Model	Concentration		References
				Control	Diseased	
TNF α	Sandwich enzyme immunoassay (EIA)	CSF	Humans (in vitro)	22.3 ± 9.5 pg/ml	96.3 ± 9.1 pg/ml	(Mogi et al. 1994)
Glutamate	Ion exchange chromatography	Blood plasma	Humans (in vitro)	34.1 ± 11.3 μmol/L	71.7 ± 8.5 μmol/L	(Iwasaki et al. 1992)
Ca^{2+}	Fluorometric analysis	Substantia nigra pars compacta	Sprague-Dawley rats. (in vitro)	0.080 μM	100 μM	(Putney and Tomita 2011)
TNFR1	ELISA	Blood serum	Humans (in vitro)	438.9 ± 171.9 pg/ml	558.5 ± 246.3 pg/ml	(de JR de Paula et al. 2009)
αS	IMR assay	Blood plasma	Humans (in vitro)	645.57 pg/ml	1294.9 pg/ml	(Oczkowska et al. 2014)
ROS	Assay for aconitase activity. Parallel assay of α-KGDH activity and H2O2 generation by α-KGDH Statistics.	Brain cortex	Guinea Pig (in vitro)	12.7 pmol/min/mg	32 pmol/min/mg	(Tretter and Dam-Vizi 2004)
IL-1β	ELISA	CSF	Human (in vitro)	9.409 pg/mL	11.122 pg/mL	(Hu et al. 2015)
Tau	Sandwich ELISA	CSF	Human (in vitro)	640 ± 230 pg/ml	720 ± 590 pg/ml	(Blennow et al. 1995)

TNFα concentration level in diseased condition was measured in the striatum and cerebrospinal fluid (CSF). The concentration in CSF was noted as 22.3 + 9.5 pg/ml in control and 96.3 + 9.1 pg/ml in patients. The feedback mechanism in the production of extracellular TNFα involves both microglial and astrocyte TNFα along with their respective TNFR1 receptors (Fig. 1).

The feedback mechanisms involving TNFα release during inflammation can be expressed using a simple feedback loop involved in the TNFα pathway. In the model, the extracellular TNFα (exTNFα) bound to microglial TNFα receptor (mTNFR1) and lead to the production of microglial TNFα (mTNFα) inside the microglia. As in experiments, the excess TNFα was modeled to be released and initiated its own microglial release. exTNFα can also bind to its receptor expressed in astrocyte (aTNFR1) and release TNFα inside astrocyte (aTNFα) which again triggers its own release. The

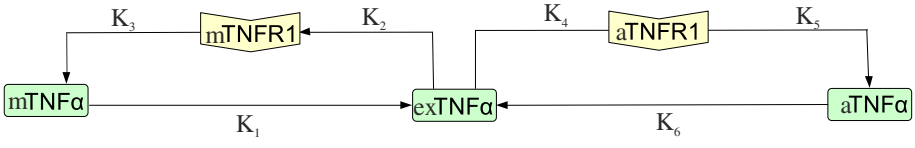

Fig. 1 The computational implementation of feedback loop in TNFα release during inflammation. Continuous activation of microglial, astrocyte and extracellular release of TNFα as the feedback mechanism expressed using a simple feedback loop. The extracellular TNFα (exTNFα) bound to microglial TNFα receptor, (mTNFR1) and led to the production of microglial TNFα (mTNFα) inside the microglia. The excess TNFα was released outside and initiated its own microglial release. exTNFα could also bind to its receptor in astrocyte (aTNFR1) and released inside astrocyte (aTNFα) which again triggered its own release

individual interactions involved were represented using mathematical equations employing kinetics law and ODE. Here, k1, k2, k3 .... k6 are the rate constants.

The individual reactions in this loop were expressed as:

$$\frac{\mathrm{d}[\mathrm{mTNFR1}]}{\mathrm{dt}} = k_2 * [\mathrm{exTNF\alpha}] - k_3\ [\mathrm{mTNF\alpha}] \tag{3}$$

$$\frac{\mathrm{d}[\mathrm{mTNF\alpha}]}{\mathrm{dt}} = k_3 * [\mathrm{mTNFR1}] - k_1\ [\mathrm{exTNF\alpha}] \tag{4}$$

$$\frac{\mathrm{d}[\mathrm{aTNF\alpha}]}{\mathrm{dt}} = k_5 * [\mathrm{aTNFR1}] - k_6\ [ex\mathrm{TNF\alpha}] \tag{5}$$

$$\frac{\mathrm{d}[\mathrm{aTNFR1}]}{\mathrm{dt}} = k_4 * [\mathrm{exTNF\alpha}] - k_5\ [a\mathrm{TNF\alpha}] \tag{6}$$

$$\frac{\mathrm{d}[\mathrm{exTNF\alpha}]}{\mathrm{dt}} = k_1 * [\mathrm{mTNF\alpha}] + k_6\ [a\mathrm{TNF\alpha}] - k_2\ [m\mathrm{TNFR1}] - k_4\ [a\mathrm{TNFR1}] \tag{7}$$

Here, extracellular TNFα (exTNFα), microglial TNFα (mTNFα), microglial TNFR1(mTNFR1), astroglial TNFα (aTNFα), astroglial TNFR1(TNFα) were the different reaction species. In a reaction, production of a new species was considered as a positive reaction whereas its degradation/release of the same/new species was a negative reaction. In this BST modelling approach, exTNFα binds to mTNFR1 that lead to the production of mTNFα inside the microglia. Here, the rate of change of mTNFR1 was mathematically represented as in Eq. (3). In the model, when mTNFR1 was considered, the reaction was exTNFα related. It bound to mTNFR1, which was a positive reaction and this led to the production of mTNFα inside the microglia which was modeled as a negative reaction. Similarly, rate changes of other reactions in the model were also converted to mathematical equations according to their rate equations. Here, Eq. (4) was the equation for mTNFα, Eq. (5) for aTNFα, Eq. (6) for aTNFR1 and Eq. (7) for exTNFα respectively. All these biochemical reactions were modelled and related concentration changes over time have been analysed. The predictions from the model were compared with previous existing reports and validated with available experimental evidence.

Pathways involved in AD and PD regulated by TNFα

Emergent properties of vicious loops in TNFα

The pathway of TNFα signalling (see Fig. 2) included some of the feedback loops and reactions involved in TNFα linked neurodegeneration. Here, activated microglia released TNFα which induced its own release and triggers glutamate release (Olmos and Lladó 2014). The excessive glutamate bound to its receptor on microglia which initiated further TNFα release in excess (Clark and Vissel 2016). In a recent study (Wang et al. 2018), on the TNFα in astrocytes to understand the multidrug resistance gene expression, activated astrocytes released TNFα and consequently it stimulated its own release. Also, it initiated astrocytes to produce excess extracellular glutamate (Mahmoud et al. 2019). In neurons, TNFα lead to excess calcium influx and initiated degeneration of the cells. The cross-talk between the dying neuron and microglia maintained activated microglia that released excess TNFα (Kuno et al. 2005; Olmos and Lladó 2014).

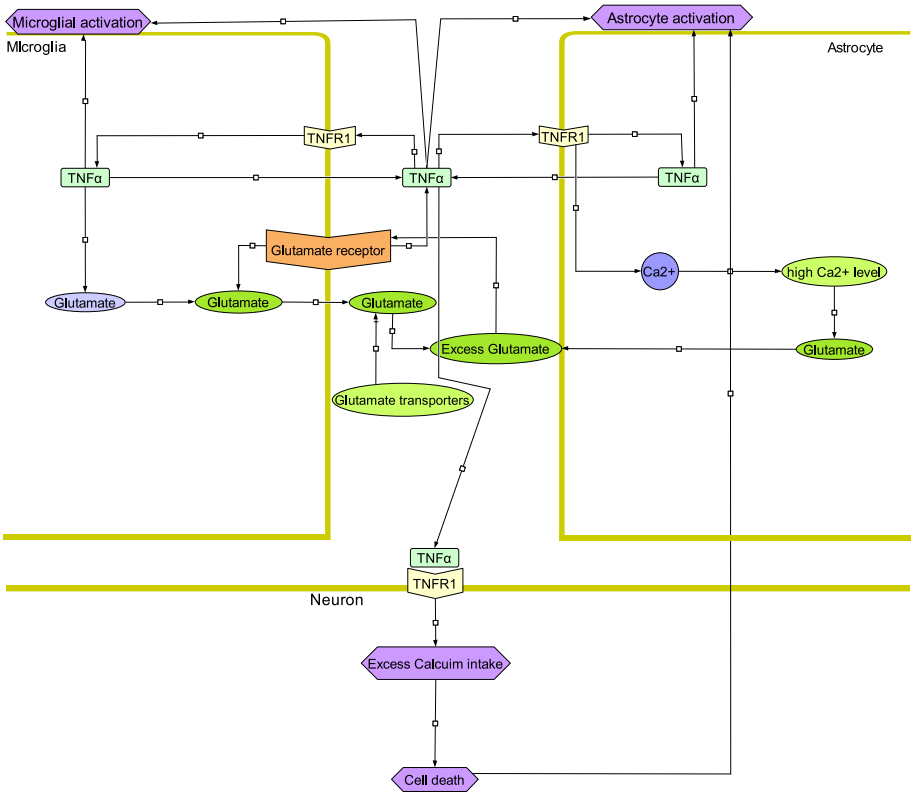

Fig. 2 Feedback loops involved in TNFα pathway related to neuroinflammation. The pathway depicts neuroinflammation induced production and release of TNFα from both microglia and astrocytes that could lead to dopaminergic cell death. Microglial release of TNFα caused its own release and initiated excess glutamate production. Excess TNFα kept microglia in the active state, which led to cellular imbalance of TNFα and glutamate. Glutamate bound to its microglial receptor and induced excess TNFα release. This prolonged activation in chronic inflammation led to rapid increase in glutamate, TNFα and other cellular factors which resulted in the damage of nearby neurons. Activated microglia also released TNFα that stimulated its own release. This initiated the production of excess extracellular glutamate that in turn induced release of TNFα. In neurons, TNFα triggers excess calcium influx which initiates pro-apoptotic factors and led to cell death. The cross-talk between the dying neuron and microglia maintained glial cells in an active state, leading to the release of TNFα

Oxidative stress in AD and PD

In our previous study (Sasidharakurup et al. 2017), we had modelled the PD-related mutated genes involved in the ROS pathway. Mutated and misfolded proteins (see Fig. 3) such as Aβ, αS and accumulation of its aggregates along with TNFα that led to the formation of ROS in AD and PD conditions were included in this model (Fischer and Maier 2015). Elevated ROS activates microglia and astrocytes. This was known to lead to cell damage and inflammation and generated a feed-forward loop of neurodegeneration (Fischer and Maier 2015). In AD, ROS activates the p38 pathway, that initiated tau phosphorylation and hyperphosphorylation that created neurofibrillary tangles, eventually leading to cell death (Niranjan 2014). In PD, αS activates the p38 pathway that induced TNFα and inflammatory cytokines in astrocytes which released cytochrome-c that produced mitochondrial oxidative stress (Yu et al. 2017). This uncontrolled process of ROS induced inflammation and TNFα-induced oxidative stress was a common pathway in neurodegeneration of neurons in both AD and PD.

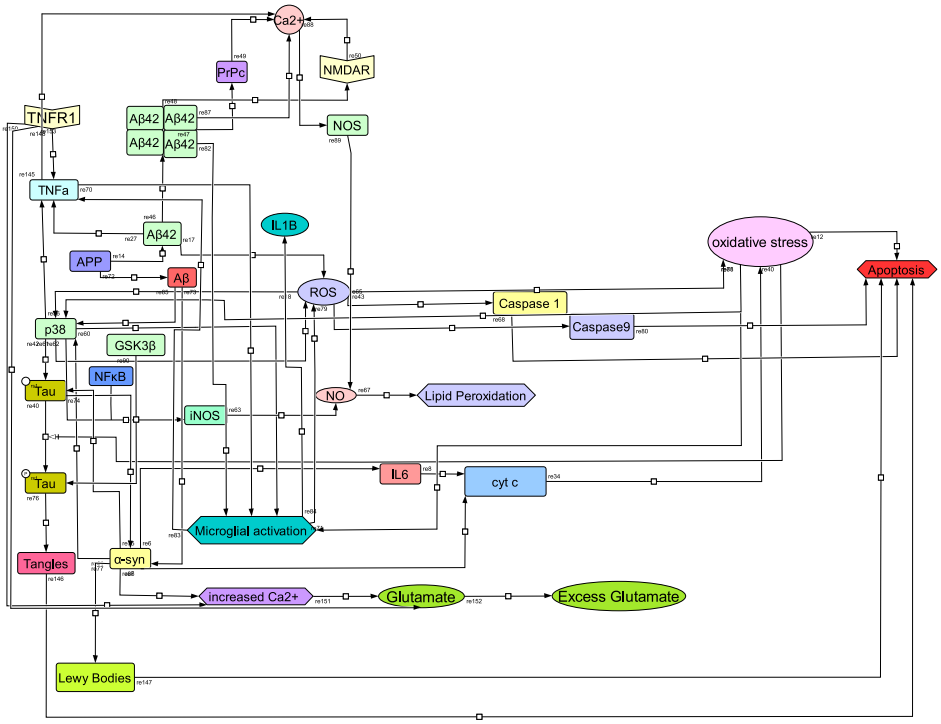

Fig. 3 TNFα induced oxidative stress lead to apoptosis in AD and PD. The oxidative pathway in the disease condition involved the role of TNFα signalling in creating oxidative stress was mapped to molecular pathways involved in AD and PD. Major mutated/misfolded protein involved in neurodegeneration such as Aβ, αS, tau which could form tangles, plaques and Lewy bodies inside the cell, may lead to the formation of ROS and create oxidative stress inside the cell disturbing other cellular reactions and signalling pathways, sharing common pathways leading to neurodegeneration. The protein aggregation and its oligomers could initiate activation of microglia and release of TNFα that may increase ROS and oxidative stress in the cell. Elevated ROS may activate microglia and astrocytes further leading to cell death and inflammation creating a feed-forward loop of neurodegeneration observed both in AD and PD conditions

Impaired insulin signalling in AD

The signalling pathway of insulin and co-related cellular reactions involved in AD and PD were also reconstructed (see Fig. 4). Under normal condition, insulin bound to insulin receptor (IR) and initiated insulin receptor substrate – 1(IRS-1) phosphorylation that triggered PI3 kinase activation (Bedse et al. 2015). This allowed signals for other cellular processes in the normal condition such as cell growth and survival. IR activation led inward and outward flow of cellular compounds in normal condition; the metabolic reactions uptook excess components or degraded it and kept the cell functioning normally (Shetty et al. 2012). In the AD brain, accumulated Aβ gets aggregated and formed oligomers that activated microglia and secreted TNFα along with other cytokines (Mandrekar-Colucci and Landreth 2012). Increased levels of TNFα and other secreted inflammatory cytokines together could inhibit the IRS-1 phosphorylation (Rehman and Akash 2016). Decreased PI3k could increase the activity of Glycogen Synthase Kinase-3 (GSK3) that resulted in phosphorylation of tau and formation of neurofibrillary tangles (Ghareeb et al. 2013). Insulin degrading enzyme (IDE) has been known to be involved in insulin and other proteasome degradation including Aβ peptide (Farris et al. 2003). Insulin resistance in the brain reduced IDE which in turn increased GSK3 activity that led to formation of tangles and gradual accumulation of Aβ. Increased

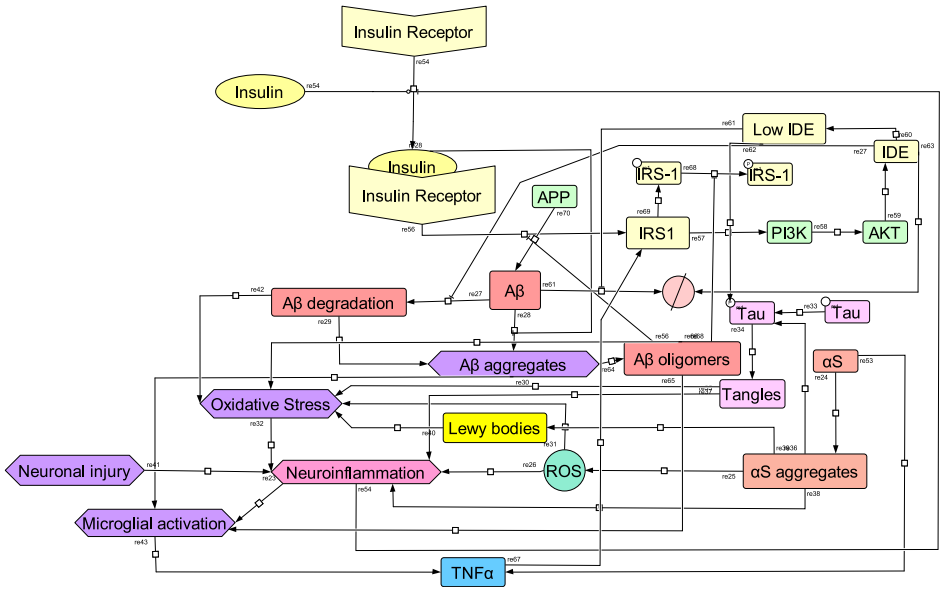

Fig. 4 Impaired insulin signalling sub-pathways in AD. Major biochemical reactions related to insulin signalling along with some of the major reactions involved in AD and PD also involve TNFα. In the AD brain, mutated Aβ gets aggregated, accumulated and forms oligomers that activated microglia that secreted TNFα along with other cytokines. Similarly, activated microglia during neuroinflammation may release the same kind of inflammatory cytokines. Both these processes can jointly increase the excess TNFα release concurrently that may inhibit the IRS-1 phosphorylation. PI3k is another factor that may result in phosphorylation of tau and formation of neurofibrillary tangles in AD. Low insulin concentration in the brain reduces the IDE, an enzyme that degrades Aβ, which in turn leads to the formation of tangles and gradual accumulation of Aβ. In AD, soluble Aβ oligomers also block IR that disturbs the normal downstream processing of insulin signalling leading to cell death. Reduced IR signalling also can affect PI3k signalling pathway and results in the upregulation of tangles and Aβ formation. This may lead to the activation of microglia by increasing the level of TNFα and other cytokines, inhibits IR, and generate oxidative stress ultimately leading to cell death

GSK3 could also activate pro-apoptotic factors leading to cell death. In AD, soluble Aβ oligomers also blocked IR that disturbed the normal downstream processing of insulin signalling leading to cell death (Arnold et al. 2018). Reduced IR signalling could also affect PI3k signalling pathway and resulted in down-regulation of glucose metabolism, upregulation of tangles and Aβ formation (Gabbouj et al. 2019). This could activate microglia by increasing the level of TNFα and other cytokines, inhibiting IR, and generated oxidative stress potentially leading to cell death.

Results

Neuroinflammation, oxidative stress and insulin signalling under normal condition

The concentration levels of TNFα, insulin, glutamate, TNFR1, calcium, ROS, αS, P38, rate of cell death and microglial activation were reconstructed (see Fig. 5). In control conditions, there was a slight increase in the level of TNFα and its surface receptor TNFR1 in the initial stage but decreased gradually over time. The level of insulin maintained at a constant level. A rapid drop in the level of excess glutamate and decrease in excess calcium influx was observed. The activation of

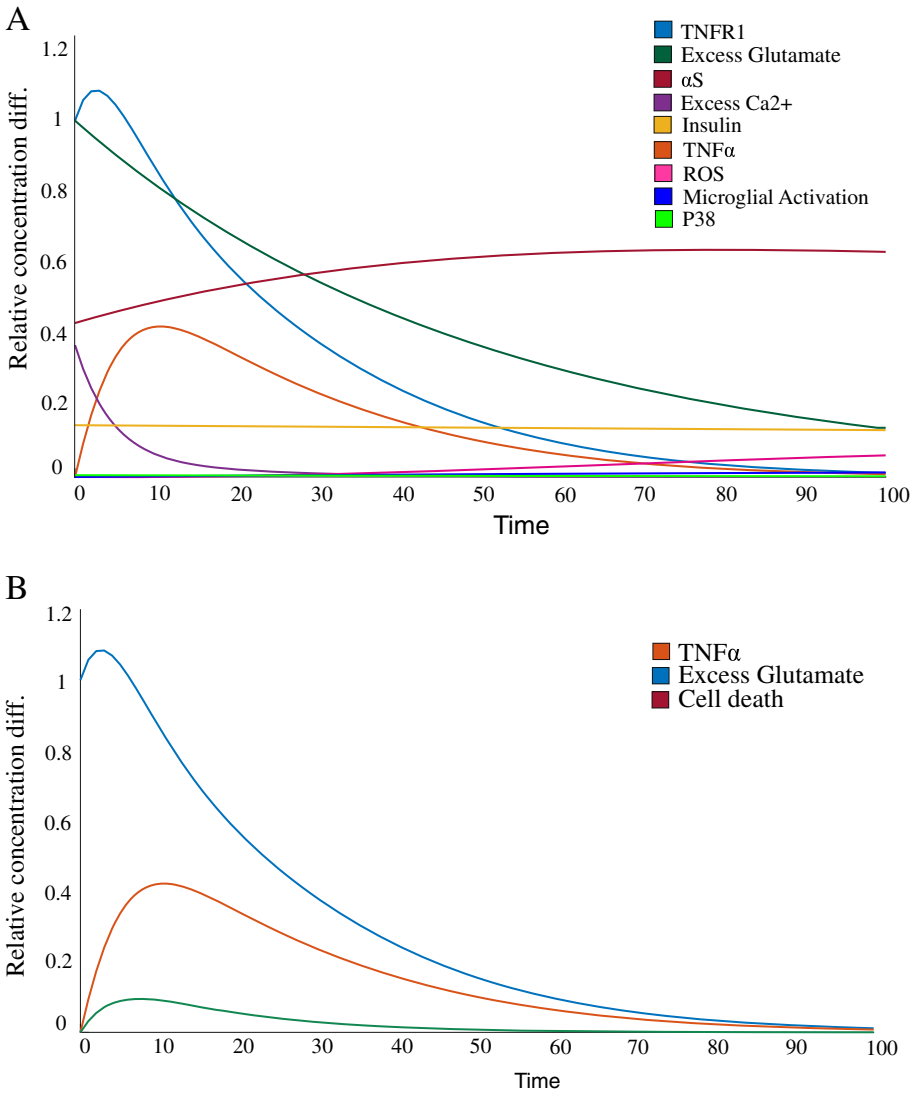

Fig. 5 Relative concentration differences in major AD/PD proteins during normal condition and variations during TNFα signalling. **a** Relative concentration differences of major proteins involved in neuroinflammation, oxidative stress and insulin signalling related to AD and PD in control condition. A slight increase in the level of TNF-α and its surface receptor TNFR1 in the initial stage was observed but decreased gradually with time. The insulin concentration was at a constant level. A sudden decrease in the level of excess glutamate and decrease in excess calcium influx. The activation of microglial rate and P38 level was comparatively low and rate of αS concentration was also consistent when compared to disease conditions. Both ROS formation and cell death rate were also negligibly less during the control conditions. **b** The relative concentration difference in TNFα, glutamate and rate of cell death in disease states. High concentration levels of TNFα and glutamate were observed compared to normal conditions. The feedback loops involved in TNFα release and microglial activation led to an increase in the concentration level of TNFα and glutamate from both astrocyte and microglia. Attributed to an increase in these factors, a high rate of cell death may be predicted in disease conditions

microglial rate was low compared in normal compared to diseased state. The rate of αS remained relatively unvarying when compared to the disease conditions. P38 level was lower and may be hypothesized as not sufficient for phosphorylation of tau protein. Both ROS formation and cell death rate were also significantly lesser in the normal condition.

Autocrine feedback loops led to continuous activation of microglia, release of TNFα and glutamate from both astrocyte and microglia leading dopaminergic cell death

The concentration differences vary across major AD/PD related proteins under normal condition and concentration variations of proteins in TNFα signalling (see Fig. 5) show a difference between states. In disease state, the concentration level of TNFα was high compared to normal conditions. The feedback loops triggering and maintaining microglial activation led to increase in the release of glutamate from both astrocyte and microglia. In disease conditions, simulations predicted elevation in the concentration of TNFα together with its receptor TNFR1.

Low concentration of insulin led to inflammation, tau hyperphosphorylation, oxidative stress that could initiate apoptotic pathway and neurodegeneration

Impaired insulin pathway in AD and PD conditions (see Fig. 6) was observed as a change in the rate of αS aggregation and Aβ plaques being elevated during diseased conditions than in normal. Insulin signalling affected the relative concentration changes in some of the key proteins involved in AD observed as a reduction in the insulin level compared to the control. Elevations in tau hyperphosphorylation could lead to the formation of neurofibrillary tangles observed during AD conditions. Compared to control, the concentration levels of αS aggregation, Lewy bodies and Aβ plaques were also high in diseased state. Since αS aggregates and Aβ plaques could promote tau phosphorylation and Lewy body formation that resulted in cell death, model replicates key players maintaining high levels of inflammation which may consequently promoted impaired insulin signalling in diseased condition and also triggered apoptotic factors that led to cell death. The relative concentration levels of ROS remain modified as tau and Lewy body levels increased suggesting elevations in protein aggregation as mechanisms led to inflammation, oxidative stress and impaired insulin signalling during AD and PD conditions.

Role of oxidative stress in TNFα signalling and microglial activation

The role of oxidative stress in TNFα signalling pathway was modelled and relative concentration differences in cellular factors involved in AD and PD was reconstructed (see Fig. 7). Elevation in the concentration levels of TNFα, inflammatory cytokines, tau protein and Aβ in AD condition when compared to normal condition. Due to this enhancement, an increased activation of microglia was observed. The elevated level of misfolded and phosphorylated tau attributed in the formation of tangles and plaques compared to control. Consequently, this resulted in an increase in NOS and ROS that led to neurodegeneration. A high level of αS aggregation was noted during the PD condition. The level of TNFα, IL-1β and release of cytochrome c was also observed. The production of ROS and microglial activation increased more than in control.

Model validation and evaluation of biological loops

Based on literature, all the connections between reactions in the modelled pathways were established and validated with published data from fluorometric analysis, ELISA, IMR assay, ion exchange chromatography, western blotting. For example, in the biochemical reactions involving TNFα induced ROS production, activation of the p38 pathway by αS induced TNFα that produced mitochondrial oxidative stress as in the experimental studies by (Schäfers et al. 2003) which shows TNFα activated p38 in rats

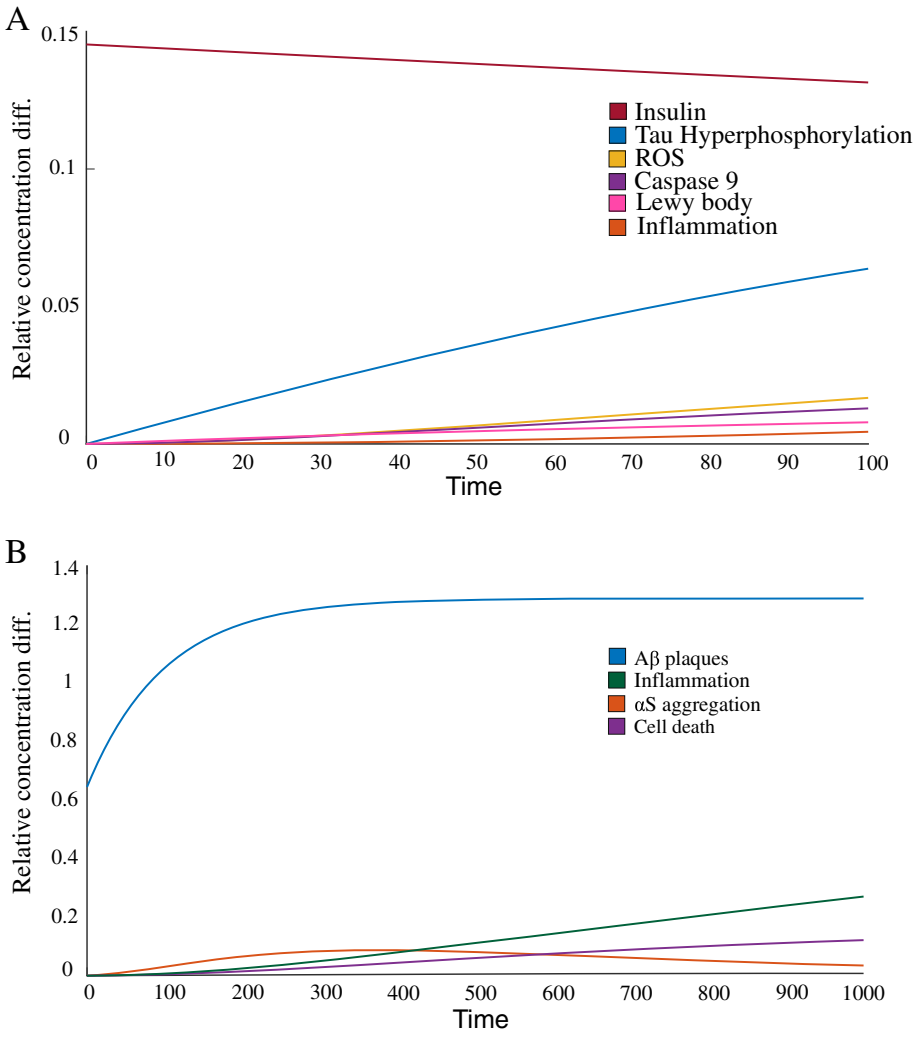

Fig. 6 Relative protein concentration changes involved in insulin impairment related to AD and PD. **a** Cellular reactions involved in inflammation and insulin signalling could affect the relative concentrationsof tau, ROS, caspases and Lewy body formation. A gradual decrease in insulin concentration level, an increase in rate of tau hyperphosphorylation, elevations in the concentration levels of caspase 9 and ROS were observed that may lead to cell death. As the concentration rate of the Lewy body increases, the concentration level of inflammation also increased. The increase in inflammation rate was noted as a reason for decrease in the level of insulin. **b** The concentration levels of αS aggregation and Aβ plaques were higher during the diseased conditions. This may attribute to the elevation in tau hyperphosphorylation and Lewy body concentration levels, perhaps leading to the high ROS production. Elevations in protein aggregation lead to inflammation, oxidative stress and impair insulin signalling during AD and PD conditions

using Western blot assays and immunohistochemistry. Another study by (Sidoti-De Fraisse et al. 1998) had shown evidence on the role of mitochondria and ROS in TNFα induced cell death. The experiment was done in HeLa cells and analyzed using flow cytometry and fluorescence methods. The model describes correlation between GSK3β and tau phosphorylation, which was validated against the experimental studies by (Duka et al. 2009), where it wass shown that GSK3β catalyses the formation of αS oligomers and these oligomers in turn helped to activate GSK3β. This activated form again helps in tau hyperphosphorylation. The inter-

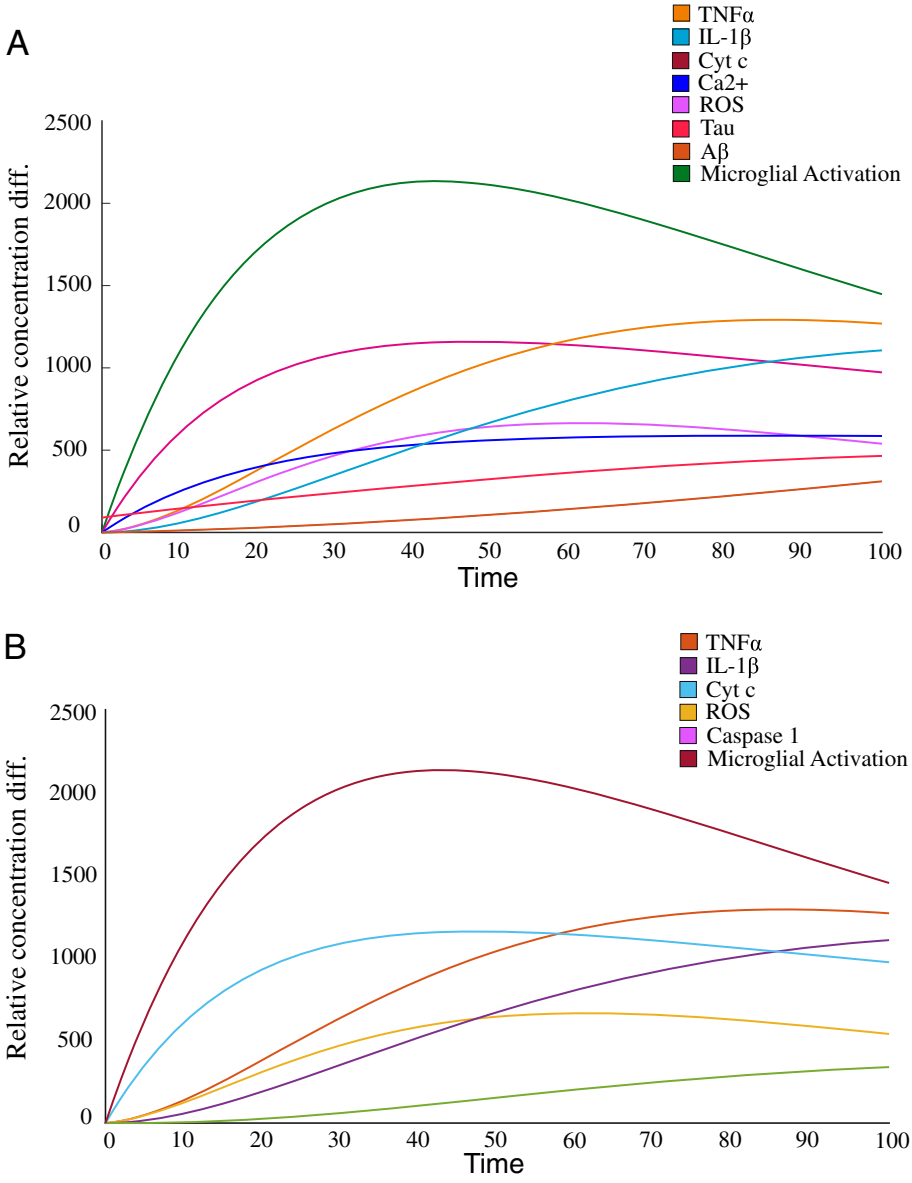

Fig. 7 Relative concentration differences in cellular factors that led to oxidative stress regulated by TNFα in AD and PD. **a** Relative concentration changes in TNFα, Il-1β, ROS, Aβ, tau, etc. could trigger oxidative stress in AD. The role of oxidative stress in TNFα signalling pathway was modelled and elevations in concentration levels of TNFα, Il-1β, tau and Aβ during AD conditions suggests an increase in microglial activation. Increased tau and calcium have also been noticed with the elevations in concentrations of TNFα and microglial activation. **b** The increase in TNFα and IL-1β was observed compared to normal conditions. This led to an increased concentration level of ROS. The increased level of caspase 1 with the increase in level of cytochrome c was noted. Both these processes may lead to cell death. Microglial activation was also high in both AD and PD conditions

relations between these proteins was demonstrated by co-precipitating α-synuclein with tau and GSK3β by GST pull down assay and western blotting (Kawakami et al. 2011). The study had reported the interaction of αS with both tau and GSK-3β. Similarly, all the interactions and correlations between biochemical reactions modelled in this study were validated by comparing with published experimental data.

Concentration variations of some of the reactions and interactions suggested by this model were validated with evidence from both existing experimental and computational models. In this model, simulation suggested high concentration levels in diseased conditions than in control. An experimental study measuring the TNFα levels in the striatum and CSF of both control and PD brains by sandwich enzyme immunoassay (Mogi et al. 1994) had reported that TNFα levels were significantly higher in PD than in control. Elevations in concentration changes of TNFα and its receptor has also been observed in this model according to the feedback mechanism that might be attributed to diseased states as observed in previous computational models (Anderson et al. 2015). Other computational models also have evidence showing increase in the extracellular TNFα and its receptor concentrations could result in negative regulation of other signaling pathways involved in inflammation and apoptosis (Fallahi-Sichani et al. 2011; Su and Wu 2020). In diseased conditions, simulations showed elevations in the concentration of TNFα together with its receptor TNFR1. Experimental studies have also observed that the feedback interaction of TNFα with its receptor TNFR1 induced its own release (Olmos and Lladó 2014). Both experimental and computational studies supported prolonged activation of microglia release proinflammatory cytokines including TNFα and interleukins that disrupted the downstream cellular signaling processes that could cause cell death as suggested in this model (A Frankola et al. 2011; Anderson et al. 2015; Cilfone et al. 2015). TNFα regulated oxidative stress response, and changes in related proteins and other factors also have been modelled and validated with existing evidence from both experimental and computational models (Braatz and Coleman 2015; Fischer and Maier 2015). Simulations suggested a low concentration of insulin led to inflammation and oxidative stress. A recent computational study by (Smith and Shanley 2013) reproduced multiple experimental observations demonstrating regulation of insulin signaling by oxidative stress that led to cell death as predicted by this model.

In this model, we had reconstructed three subnetworks associated with TNFα signalling (inflammation, oxidative stress and insulin signalling), where the emergent properties of these subnetworks could developed the onset and progression of AD and PD. The critical reactions associated with these subnetworks included abnormal aggregations of αS, Aβ and tau, the major cellular components associated with the pathophysiology of both AD and PD. The simulations suggested abnormal aggregation of these proteins along with TNFα could induce oxidative stress, inflammation and insulin resistance in the brain. Simulations showed high concentration levels of αS aggregation and Aβ plaques during diseased conditions. Aggregation and oligomerization under varying concentrations of reactants were modeled. The concentration levels of Aβ plaques, aggregation of αS and tau hyperphosphorylation increased with respect to time in diseased conditions compared to control, as observed in experiments, suggesting the robustness of this model. The concentration change could further lead to inflammation, oxidative stress and insulin resistance that in turn released excess TNFα initiating stress and inflammation creating a feedback loop of neurodegeneration as observed in experimental studies (Mandrekar-Colucci and Landreth 2012; Fischer and Maier 2015).

Discussion

Although the role of TNFα pathways were independently associated with neuroinflammation, oxidative stress and insulin signalling, the involvement of autocrine loops and

interdependency of biochemical reactions and their correlations in disease onset and progression, as modeled in this study, are critical to understand AD, PD and neurodegeneration.

In this study, the contribution of cellular reactions involved in the pathways related to the neurodegeneration processes that leads to Alzheimer's and Parkinson's have been modelled to understand the emergent properties. The modelling shows that mutations in some of the proteins such as αS, Aβ and tau share common pathophysiology in both AD and PD. These proteins along with TNFα, ROS and other kinases can induce oxidative stress in neurons that trigger apoptotic pathways. Simulations suggested insulin was a key factor that could trigger and modulated common signalling pathways observed in AD and PD such as neuroinflammation and oxidative stress. It is also associated with the variations in cellular concentrations of αS, Aβ and tau and led to accumulation of toxic cellular oligomers.

Several factors led to microglial activation. and included TNFα, suggesting the role of TNFα-induced neuroinflammation in activation of glial cells that lead to neurodegeneration. The simulations also highlight feedback loops, oxidative stress and insulin pathway in the brain regulated by TNFα. Feedback interaction of TNFα with its receptor TNFR1 induced its own release matching experimental studies (Olmos and Lladó 2014). Increased concentrations in TNFα and its receptor due to the feedback mechanism could be attributed to diseased states. Increases in the level of TNFα in the model led to production of excess glutamate that consequently led to an increase in TNFα concentration level has been observed.

In neurological conditions, simulations suggested a prolonged activation of microglia. Although TNFα and other cytokines come to homeostasis inside cells in time, glial cells can stay active for a longer period. In diseased condition, this prolonged activation of microglia may lead to a release of proinflammatory cytokines including TNFα and interleukin 6 beta (IL-6β) that could disrupt the downstream cellular signalling processes leading to cell death as suggested in experiments (A Frankola et al. 2011). Like relevant clincal markers. Simulations showedelevated levels of mutated AD and PD related protein aggregation in diseased conditions compared to normal conditions. A high level of αS, Aβ and tau protein; key factors in the formation of fibrils, plaques and tangles were related and could induce oxidative stress in the cell. Increase in concentration levels of TNFα, IL-1β and calcium levels have also been observed in diseased conditions. This could be the attributed cause of activating microglia and could lead to production of TNFα and IL-1β, as indicated in simulations.

The insulin signalling pathway in the brain is regulated by cross-talk between several other signalling pathways including TNFα signalling leading to neuroinflammation and oxidative stress. Along with major mutated proteins in AD/PD such as αS, Aβ and tau, dysregulation in these signalling pathways can cause an insulin resistance in the brain. The results also have shown an increased level of ROS in diseased state. The simulations suggest low insulin could lead to high inflammation rate, oxidative stress and cell death when compared to control. It may be predicted that TNFα, ROS and insulin act as reliable biomarkers for both PD and AD.

The control condition may be indicative of the relative concentration changes in TNFα, insulin, glutamate, TNFR1, calcium, ROS, αS, P38, microglial activation and rate of cell death. This may be used as a prediction template for AD/PD relating conditions of neuroinflammation, oxidative stress and insulin resistance. When compared to diseased state, rate of microglial activation, αS, Aβ, P38, ROS formation and cell death rate, tau hyperphosphorylation, oxidative stress and cell death were considerably low.

Given all the three conditions (inflammation, oxidative stress and insulin resistance), diseased state can be identified with high concentration elevations in TNFα, αS, Aβ and tau compared to control. Given the correlations among the feedback loops, PD can be distinguished from normal conditions through high relative concentration differences in TNFα, glutamate, calcium and rate of cell death during neuroinflammation compared to control. In diseased state models associated with oxidative stress, there could be high activation of microglia, increased concentration levels of calcium, ROS, cytochrome c, and proinflammatory caspases was observed compared to control. Insulin involvement in disease state can be identified with high inflammation rate, oxidative stress and cell death compared to control.

The predictions relate experimentally observed concentrations to parameters seen during clinical measurements. The study correlated Aβ toxicity to potential clinical features such as delusions, hallucinations, seizures attributed with tau toxicity. This matches with recent studies; both familial and sporadic PD patients report symptoms related genes indicating abnormal accumulation of αS, Aβ, tau toxicity and other neuroinflammatory cytokines as mentioned in this model and hence the model can be used to predict changes in biomarkers for both prodromal and preclinical diagnosis of the disease (Popescu 2016; He et al. 2018). This model may serve as a design framework for altering experimental interventions. Although cerebro-spinal fluid was the main source of data for several parameters related to initial conditions, given the predictions from the data it may relate to changes in substantia nigra, blood, serum, blood plasma, brain cortex and hippocampus for labelling and further analysis.

Conclusion

This study extends current modeling studies on TNFα mediated glutamate excitotoxicity and neuroinflammation in PD, and a computational model to analyse TNFα signalling pathway was reconstructed to understand how inflammation, oxidative stress and insulin resistance are related to each other in neurodegeneration developing diseases such as AD and PD. The model closely reconstructs known pathways of biomarkers of chronic neuroinflammation, oxidative stress and insulin signalling that are co-involved in AD and PD. Validation of the autocrine loop-related predictions need further laboratory experiments to be carried out and mapping symptoms to concentration changes that may need an extensive analysis of model's biochemical reactions and their disruptions leading to neurodegeneration.

Abbreviations

AD: Alzheimer's disease; PD: Parkinson's disease; TNF彬: Tumour Necrosis Factor alpha; Aβ: Amyloid β-peptide; αS: Alpha synuclein; BST: Biochemical systems theory; ODE: Ordinary differential eqs.; MM: Michaelis-Menten; GMA: Generalized Mass Action; CSF: Cerebrospinal fluid; exTNFα: Extracellular TNFα; mTNFR1: Microglial TNFα receptor; mTNFα: Microglial TNFα; aTNFR1: Astrocyte TNFα receptor; aTNFα: Astrocyte α; ROS: Reactive oxygen species; NOS: Nitrogen oxygen species; IR: Insulin receptor; IRS-1: Insulin receptor substrate − 1; GSK3: Glycogen Synthase Kinase-3; IDE: Insulin degrading enzyme; IL-1β: Interleukin 1 beta

Acknowledgments

This work derives direction and ideas from the Chancellor of Amrita Vishwa Vidyapeetham, Sri Mata Amritanandamayi Devi. The authors acknowledge undergraduate student interns, Kanishka Bhaskar, Lakshmi Nair, Meera Nair, Namitha Nalarajan, Arathy Koranath and Shibin Mubarak for their contributions in this article.

Authors' contributions

Conceived and developed the method: HS, SD. Analyzed the data: HS, SD. Wrote the paper: HS, SD. All authors read and approved the final manuscript.

Funding
This study was partially supported by the Department of Science and Technology Grant DST/CSRI/2017/31, Government of India.

Competing interests
The authors declare that they have no competing interests.

Received: 22 April 2020 Accepted: 12 August 2020
Published online: 25 September 2020

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