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A Quantitative Analysis of Insulin Signaling in Neurodegeneration

A thesis submitted in partial fulfillment of the requirement for the degree of Bachelor of Science in Neuroscience from The College of William and Mary

by

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Abstract

This project introduces two mathematical models representing the biochemical interactions between insulin signaling, PD, and AD. The models can be used to examine the changes that occur over the course of the disease as well as identify which processes would be the most effective targets for treatment. The models are mathematized using Biochemical Systems Theory. They incorporate treatment strategies that includes several experimental drugs along with current treatments. In the past, BST models of neurodegeneration have used Power Law Analysis and Simulation to model the system. This work recommends the use of MATLAB instead. MATLAB allows for more flexibility in both the model itself and in data analysis. Previous BST analyses of neurodegeneration began treatment at disease onset. As shown in these models, the outcomes of delayed, realistic treatment and full treatment at disease onset are significantly different. The delayed treatment strategy is an important development in BST modeling of neurodegeneration. It emphasizes the importance of early diagnosis, and allows for a more accurate representation of disease and treatment interactions.

1. Introduction

PD is a neurodegenerative disorder characterized by dopaminergic neuron death in the substantia nigra pars compacta and results in physical symptoms such as tremors, rigidity, and bradykinesia as well as psychological symptoms such as an increased risk of dementia, depression, and anxiety. Insulin resistance, a precursor of T2DM, is a result of a diet high in fats and sugars. Insulin signaling pathways and PD pathogenesis have been experimentally proven to converge (Morris et al., 2008; Morris et al., 2011), yet clinical data is inconsistent (Bosco et al., 2012). The model includes production of ROS and RNS, p38 phosphorylation, tau protein
hyperphosphorylation, inflammation, and dopamine synthesis, degradation, and transport. This paper presents a mathematical model that details the interactions between these processes and how they can combine to influence neuronal death.

AD is an age-related neurodegenerative disorder affecting many brain regions, notably the cholinergic neurons in the hippocampus, which are correlated to the cognitive decline characteristic of AD (Kerbler et al., 2015). Insulin resistance in AD is much more accepted than in PD. Both a lack of insulin in the CNS, similar to T1DM, and a lack of CNS insulin receptor sensitivity, similar to T2DM, have been associated with AD, leading some to suggest that AD should be known as “type-III diabetes” (de la Monte et al., 2014). This paper presents a model of the pathways shared between insulin signaling impairment and AD within cholinergic neurons, astrocytes, and microglia. The data presented focuses on changes in insulin signaling, inflammation, ROS production, mitochondrial dysfunction, Ca2+ signaling dysregulation, neurofibrillary tangle production, Aβ oligomerization, p38 activation, and finally cell death.

These disease simulations make use of a modeling strategy known as BST, which was established by Savageau in 1969 and developed further by Voit in 2000. BST uses ODEs to model changes in reaction rates and species concentrations throughout the progression of the disease. These models include a baseline state, which depicts a healthy cell, a disease state, modeling a cell with PD and insulin resistance, and a treatment state, which is a disease state cell including several treatment options. The disease state was created by activating trigger points within the baseline model that initiated disease development, and the treatment state was created by introducing a mixture of drugs at two times: the onset of the disease, and halfway through the
disease progression. These treatments target reactions the models show are important in neurodegenerative pathogenesis where it converges with insulin signaling pathways.

2. Methods

2.1 Modeled Pathways in PD

This section explains several key pathways in the model, demonstrating the extent to which insulin signaling influences the biochemistry of PD. The system was modeled using the biochemical pathway visualization program CellDesigner.

2.1.1 Insulin Signaling and Inflammation

Insulin signaling begins with insulin binding to the insulin receptor on the cellular membrane, which causes phosphorylation of the insulin receptor substrate (Takahashi et al., 1996). Insulin signaling is promoted by PPARG, which is also a transcription factor for proteins important in antioxidant scavenging and mitochondrial repair (Miranda et al., 1999; Mudo et al., 2012; Xing et al., 2007). Insulin signaling is inhibited by the chronic inflammation present in PD. The inflammation is a result of cytokine production in astrocytes and microglia, specifically cytokines IL-1β, IL-6, TNFα, and MCSF (Ghosh et al., 2007; Glass et al., 2010). Overproduction of NO promoted by nitric oxide synthase (Hunot et al., 1996), prostaglandin synthesis promoted by COX2 (Xing et al., 2007), and NF-κB in the neuron and glia are also contributing factors. Inflammation is decreased by the presence of PPARG (Ricote et al., 1998). This process is outlined in Model 1.
2.1.2 Dopamine

Dopamine is produced in the neuron through the conversion of tyrosine to L-DOPA, and L-DOPA to dopamine (Model 2). Tyrosine hydroxylase, which is activated via phosphorylation by phosphorylated p38, promotes L-DOPA synthesis, and decarboxylase promotes the final step in the process to produce dopamine (Yu et al., 2005). Dopamine can also enter the cell through the dopamine transporter, which is upregulated by insulin signaling (Patterson et al., 1998). Free dopamine in the cell can be degraded into quinones, H2O2, and O2- (Yu et al., 2005), or use a

Model 1: Mechanisms of inflammation and factors influencing insulin signaling in PD
monoamine oxidase promoter, producing \( \text{H}_2\text{O}_2 \) and DOPAL (Marchitti et al., 2007). Alternatively, dopamine is collected into vesicles to be released at synapses. Vesicular dopamine is protected from degradation and the resulting production of ROS. VMAT are important in sequestering the dopamine into vesicles. VMAT is downregulated in PD (Xiong et al., 2011).

**Model 2:** Reactions and cellular processes involving dopamine in PD
2.1.3 ROS and RNS

ROS are the result of dopamine degradation and mitochondrial dysfunction in PD. Mitochondrial dysfunction creates an excess of O$_2^-$, which can be converted to H$_2$O$_2$ by SOD2. The H$_2$O$_2$ can then be converted to water by glutathione or catalase (Evans et al., 2002), or OH- by Fe through the Fenton reaction. Dopamine degradation also produces H$_2$O$_2$ and O$_2^-$ in the cell. NO, a RNS, is produced in both the neuron and the glia from L-citrulline, and is membrane-permeable (Hunot et al., 1996). The NO can react with O$_2^-$ to create ONOO-, which is extremely dangerous to the neuron (Beckman, Crow, 1993). Excessive ROS and RNS can react easily with vital cellular species causing lipid peroxidation, misfolded proteins, DNA damage, and endoplasmic reticulum and mitochondrial stress, all of which decrease cellular function and increase the risk of cell death. ROS and RNS can also trigger the caspase cascade, initiating apoptosis (Choi et al., 2004; Ko et al., 2005).

Model 3: Synthesis and degradation of reactive oxygen and nitrogen species in PD
2.1.4 Tau Phosphorylation, Neurofibrillary Tangles, and Lewy Bodies

Insulin signaling phosphorylates PI3K (Piao et al., 2012), which in turn phosphorylates PIP2, creating PIP3. PIP3 deactivates GSK-3β through phosphorylation, which prevents it from promoting tau hyperphosphorylation (Lucas et al., 2001). Tau hyperphosphorylation is also promoted by phosphorylated p38 (Zarubin, Han, 2005). The tau protein is important in microtubule stabilization, so the loss of function caused by the hyperphosphorylation results in impeded axonal transport. Hyperphosphorylated tau is a component of aggregates such as neurofibrillary tangles and Lewy bodies, which are characteristic of PD (Arima et al., 1999; Bancher et al., 1993). Lewy bodies also contain proteins such as parkin and α-synuclein, which aggregate as a result of ROS interactions that cause them to misfold (Winklhofer et al., 2003; Zheng et al., 2010).

Model 4: The effects of insulin resistance on tau hyperphosphorylation, neurofibrillary tangle accumulation, and Lewy body production in PD
2.1.5 p38 Phosphorylation

The p38 mitogen-activated protein kinase is involved in several different pathways in this model. p38 is activated by phosphorylation, which is promoted by prostaglandins, tumor necrosis factor α receptor 1 signaling, and ROS (Choi et al., 2004). Inhibition of p38 phosphorylation is caused by insulin signaling (Heidenreich, Kummer, 1996) and the MKP-1 expressed by the DUSP1 gene (Taylor et al., 2013). p38 promotes caspase 9 maturation leading to apoptosis, tau phosphorylation, tyrosine hydroxylase activation, Bax/tBID complex formation resulting in mitochondrial membrane depolarization and related dysfunction, and finally Hsp27 activation

Model 5: Mechanisms influencing p38 phosphorylation and its effects on the cell in PD
(Snyder et al., 2009; Yu et al., 2005; Zarubin, Han, 2005). Hsp27 can inhibit tau phosphorylation, increase glutathione expression, inhibit Fas ligand binding, and decrease Lewy body formation by preventing α-synuclein aggregates from accumulating in the Lewy bodies (Choi et al., 2012; Mehlen et al., 1996; Mehlen et al., 1996a; Shimura et al., 2004; Zourlidou et al., 2004). p38 can also be ubiquitinated by the E3 ubiquitin ligase parkin and degraded (Ko et al., 2005). Parkin is downregulated in PD which causes an increase in p38.

2.1.6 Cell Death

Cytosolic ROS can directly cause apoptosis by activating the caspase cascade (Choi et al., 2004; Ko et al., 2005), and mitochondrial ROS can indirectly activate the caspase cascade by opening the PTP of the mitochondria and releasing cytochrome c (Moon et al., 2005), SMAC/DIABLO, and AIF. SMAC/DIABLO increases caspase activity by binding to IAP proteins, which prevent the IAP from binding to and inhibiting caspases 3 and 9. Cell death can also be triggered in a caspase-independent manner by DNA fragmentation and chromosome condensation initiated by

![Model 6: Cellular processes contributing to the death of SNPC neurons in PD](image-url)
the migration of the AIF from the mitochondria to the nucleus (Susin et al., 1999). Furthermore, hyperphosphorylated tau can create neurofibrillary tangles and Lewy bodies, inducing cell death.

2.2 Modeled Pathways in AD

An explanation of central pathways in the model, showing circumstances in which insulin signaling influences the pathology of AD. The system was modeled using the biochemical pathway visualization program CellDesigner.

Model 7: Insulin signaling and inflammatory pathways in AD
2.2.1 Insulin Signaling and Inflammation

Insulin signaling in Alzheimer’s disease (Model 7) begins when an insulin molecule binds to the insulin receptor, which activates the insulin receptor substrate and begins a signaling cascade. In addition to insulin resistance from inflammation, as seen in Parkinson’s disease, amyloid beta oligomers can interfere with insulin signaling by interacting with insulin receptors and preventing insulin from reaching the receptor (DiCarlo et al., 2010). Microglia and astrocytes play a major role in the inflammatory process in Alzheimer’s disease through the activation of NF-κB, a transcription factor that promotes the expression of inflammatory cytokines including IL-6, IL-1β, and TNFα (Hayashi et al., 1993). NF-κB also promotes the expression of the enzymes iNOS and COX2, which catalyze reactions that produce NO and O2-, respectively (Arias-Salvatierra et al., 2011; Chandel et al., 2000; Cogswell et al., 1994; Heyen et al., 2000; Kaltschmidt et al., 2002; Van Wagoner et al., 1999). These reactive molecules also contribute to inflammation (Glass et al., 2010; Mander et al., 2005).

2.2.2 ROS and Mitochondrial Dysfunction

NO created by iNOS during the inflammatory process (Model 8) is able to diffuse across cell membranes and react with O2- in the neuron, creating the highly toxic ROS ONOO- (Beckman, Crow, 1993). The O2- can also degrade into H2O2, and subsequently OH-, both of which are also harmful, or instead from H2O2 to water in the presence of glutathione (Evans et al., 2002). The primary source of O2- is the mitochondria, where it is produced in small amounts during normal respiratory functions. During mitochondrial dysfunction, especially in the respiratory complex I, larger amounts of O2- are formed (de la Monte et al., 2014). This oxidative stress in turn creates further dysfunction in complex I, which can then lead to mitochondrial membrane
depolarization. When the mitochondrial membrane is compromised, the H+ ions can leak through, and the H+ gradient that drives ATP-synthase is weakened, causing ATP depletion. Without ATP, the cell has no way of transferring energy and will soon die. (Atlante et al., 2008). Mitochondrial membrane depolarization can also be triggered by the truncation of the mitochondrial membrane protein BID by the proteins caspase 8 and calpain (Di Carlo et al., 2010; Kelly et al., 2006; Snyder et al., 2009).

**Model 8**: Reactive oxygen species synthesis and causes and consequences of mitochondrial dysfunction in AD

### 2.2.3 \( \text{Ca}^{2+} \) Dysregulation

\( \text{Ca}^{2+} \) is an important signaling molecule in neurons, but can be harmful at high concentrations. \( \text{Ca}^{2+} \) usually enters the cytosol from the extracellular environment (Model 9). \( \text{Ca}^{2+} \) is also sequestered in the endoplasmic reticulum. During endoplasmic reticulum stress, which can be


**Model 9: Causes and consequences of abnormal Ca2+ signaling in AD cells**

triggered by events such as an accumulation of misfolded proteins, the Ca2+ stores can be released (Casley et al., 2009; Katayama et al., 2004). During Alzheimer’s disease conditions, Aβ oligomers can interact with the Ca2+ voltage-gated ion channels and NMDA receptors to dysregulate Ca2+ signaling (DeWachter et al., 2009; Mota et al., 2014; Nicholson et al., 2009; Snyder et al., 2005; Wang et al., 2005). Once Ca2+ levels in the cytosol become too high, the Ca2+ can activate the protein calpain, which can increase the accumulation of both Aβ oligomers and neurofibrillary tangles (Goñi-Oliver et al., 2007; Kelly et al., 2006). The Ca2+ can also enter the mitochondria, which it can activate NADPH oxidase, which promotes the formation of O2 during the oxidation of NADPH to NADP+, contributing to mitochondrial dysfunction (Stutzmann, 2007).
2.2.4 Neurofibrillary Tangles

Neurofibrillary tangles are comprised primarily of hyperphosphorylated tau proteins, which usually function to stabilize the cytoskeletal microtubules (Model 10). When the tau are hyperphosphorylated, however, they release from the microtubules and aggregate into neurofibrillary tangles. Calpain, p38, and GSK-3β, which is inhibited by the insulin signaling kinase cascade, can all contribute to tau hyperphosphorylation (Johnson et al., 1989; Li et al., 2003). Once the tau proteins are phosphorylated, inflammatory conditions create an environment suitable to aggregation (Liu et al., 2014). Phosphorylated insulin receptor substrate can also relocate from the nucleus to colocalize with neurofibrillary tangles. Aβ oligomers can activate

**Model 10:** Neurofibrillary tangle production and triggers in AD
the nuclear protein Jun, which then phosphorylates the insulin receptor substrate (Ma et al., 2009).

2.2.5 β-secretase and Aβ Oligomers

APP expression is promoted by IL-1β signaling from the glia during inflammation (Model 11). IL-1β also increases the rate of APP cleavage into Aβ fragments, which is catalyzed by the enzyme β-secretase (Li et al., 2003). β-secretase expression is promoted by NF-kB in neurons during Alzheimer’s disease conditions, as well as by inflammation (Bourne et al., 2007; Heneka et al., 2005). Once it is created, it can then be activated by calpain after Ca2+ dysregulation (Goñi-Oliver et al., 2007). Aβ oligomerization is promoted by GSK-3β, which is inhibited by insulin signaling. Once the Aβ oligomers are created, however, they inhibit further insulin signaling (Di Carlo et al., 2010). Aβ oligomers have recently been identified as the toxic species of Aβ in Alzheimer’s disease instead of plaques. They contribute to further Ca2+ dysregulation

Model 11: Production of activated beta secretase and consequent formation of amyloid beta oligomers and onset of their toxic effects in AD
as previously discussed. Lysosome permeability occurs when the lysosomes attempt to degrade A\(\beta\) but become overwhelmed. This releases other toxic lysosomal content into the cytosol causing further stress to the cell (De Kimpe et al., 2013).

### 2.2.6 p38 Phosphorylation and Cell Death

The protein p38 plays multiple roles in initiating apoptotic processes in distressed cells. It can be inhibited by insulin signaling, but activated by inflammation via IL-1\(\beta\) as well as the ROS NO and O\(_2^-\) (Li et al., 2003). p38 blocks synaptic signaling by preventing the actions of the synaptic protein synaptophysin. It also acts to phosphorylated tau, contributing to the production of neurofibrillary tangles. It also converts procaspase 9 to caspase 9, which then joins the apoptosome and triggers apoptosis, as well as converts procaspase 8 to caspase 8, causing

**Model 12**: Cellular processes contributing to p38 phosphorylation and neuronal death in AD
mitochondrial stress (Di Carlo et al., 2008). Cell death can be caused by many of the processes controlled by p38, including ROS from mitochondrial dysfunction, neurofibrillary tangle buildup, and apoptosis (Liu et al., 2014; Mota et al., 2014). Endoplasmic reticulum stress from Ca2+ dysregulation and lysosome permeability from Aβ oligomer degradation attempts are also contributing factors (De Kimpe et al., 2013; Katayama et al., 2004).

2.3 Biochemical Systems Theory

The system was mathematized using BST to create a dynamic model in MATLAB of the species concentrations and reaction rates as they change over the course of the disease. For further information on the use of BST to model neurodegenerative disease systems using PLAS, see this lab’s previous work (Broome, Coleman, 2011; Sass et al., 2009; Yeager, Coleman, 2010).

2.3.1 Initial Values

Initial values are assigned to both independent and dependent variables. Independent variables are species that are not the products of any process or reaction in the system, whereas dependent variables are the product of at least one process or reaction. The values are assigned on a relative rather than absolute basis which allows for the estimation of unknown values. When available, values from the literature are taken into consideration and adapted to the relative scale.

2.3.2 Flux Equations

Flux equations, each of which is assigned a location in the matrix J, describe the relative reaction rates. Each flux equation takes into account the concentrations of the reactant species and a rate constant or rate equation. Every reaction or process in the model is assigned a flux equation.
equations take the following form: \( J(88) = X(258)\times X\text{ind}(75) \). In this case, \( J(88) \) represents L-DOPA synthesis, the 88\textsuperscript{th} value in \( J \). \( X\text{ind}(75) \) represents the independent variable tyrosine, and \( X(258) \) represents the rate ODE. Rate equations consist of a constant multiplied by the sum of all promoters and inhibitors, where promoters have positive concentration values and inhibitors have negative concentration values. In this case, \( X(258) = 0.0001\times X(92) \), where \( X(92) \) represents the promoter phosphorylated tyrosine hydroxylase. In the event that a reaction or process does not include any promoters or inhibitors, a rate constant, specified as a value in the array \( k \), is included instead. An example of an unmodified reaction is the equation for the formation of the IAP inhibition complex: \( J(96) = k(54)\times X\text{ind}(82)\times X(102) \), where \( k(54) \) is the rate constant, \( X(102) \) is cytosolic SMAC/DIABLO, and \( X\text{ind}(82) \) is IAP.

2.3.3 Systems Equations

Each dependent variable is assigned a systems equation, which describes the relative concentration of the species. Systems equations consist of the sum of all the flux equations in which the dependent variable is a reactant subtracted from the sum of all flux equations in which the dependent variable is a product. For example, \( X(93) = X(258)\times X\text{ind}(75) - X(259)\times X(93) \), where \( X(93) \) represents L-DOPA, \( X(258)\times X\text{ind}(75) \) represents L-DOPA synthesis from tyrosine, and \( X(259)\times X(93) \) represents dopamine synthesis from L-DOPA.

2.3.4 Data Analysis

This system exists in three states: a baseline state, a disease state, and a treatment state. In order to analyze the effects of neurodegeneration on the system, the baseline state is subtracted from the disease state so that any species with a positive value is elevated during the disease and any
species with a negative value means the species is less present in neurodegeneration. The treatment state is compared to the baseline state in the same manner. Two treatment states, one in which the treatment is introduced at disease onset, and one in which treatment is introduced halfway through disease progression (t = 75), are created. This delay is a novel technique in the evaluation of treatments in neurodegeneration using BST, and provides significant insight into the efficacy of the treatment states. The delay is a more realistic simulation of the effects the treatments will have on the patient, as diagnosis and subsequent treatment at disease onset is unlikely to occur. The comparative disease state and two comparative treatment states are then

![Graph showing Insulin Signaling in PD](image)

**Figure 1: Insulin Signaling in PD** A comparison between a Parkinson disease model that initially includes insulin resistance and one that begins with normal insulin signaling.
graphed together in order to assess the impact of the treatment strategy on the disease both in the best-case scenario and the more realistic scenario.

3. PD Results

3.1 Insulin Signaling and Inflammation

3.1.1 Disease State

Insulin signaling is impaired by decreasing the rate at which it binds to the insulin receptor. The relative concentration of the insulin receptor complex continues to decrease as the disease progresses. Normal insulin signaling also decreases compared to the baseline in response to the

![Graph showing the impact of treatment on inflammation]({image1})

**Figure 2: Inflammation in PD** An increase in inflammation which is to some extent corrected by the treatment state.
effects of PD (Fig. 1). Inflammation increases in the PD state compared to the baseline state as a result of an increase in ROS, NF-κB signaling in the astrocytes and microglia, and cytokine expression (Fig. 2).

3.1.2 Treatment State

The lack of insulin signaling is partially corrected for by the inclusion of pioglitazone and sodium butyrate, which act as insulin sensitizers (Gao et al., 2009; Hu et al., 2013). Insulin signaling is fully recovered in the model when it is initially at normal levels, and is significantly recovered in the insulin resistant model as well during full treatment (Fig. 1). With a delayed initiation of treatment, insulin signaling in both the initially insulin resistant and initially insulin sensitive models are partially corrected but continue on a downward trend. Treatments of vitamin D (Chang et al., 2004), NAC, and aspirin (Ambhore et al., 2014) correct inflammation. Vitamin D inhibits NOS from producing pro-inflammatory NO in the glia. NAC inhibits NF-κB from entering the nucleus (Oka et al., 2000), thereby reducing expression of inflammatory cytokines. NAC also acts as a COX2 inhibitor, reducing the production of prostaglandins. Aspirin acetylates COX2, inhibiting its function as a promoter of prostaglandin synthesis. The decrease in cytokine, NO, and prostaglandin concentrations accordingly decrease inflammation, although inflammation is still largely present (Fig. 2). The full treatment state was similar to the delayed state in the prevention of inflammation.
3.2 Dopamine

3.2.1 Disease State

Dopamine levels are manipulated in the disease state by decreasing the concentration of VMAT transporters that allow the dopamine to be sequestered into vesicles. Extracellular dopamine concentrations are reduced to account for the degeneration of nearby dopaminergic neurons from PD, thereby reducing intercellular dopamine signaling. Dopamine degradation rates are increased in the disease state. Cytosolic dopamine levels actually increase in the PD model (Fig. 3); however, vesicle dopamine is decreased (Fig. 4). Cytosolic dopamine is undesirable in the cell.

Figure 3: Cytosolic Dopamine in PD Increased levels of cytosolic dopamine levels which are eventually fully rectified in the treatment state.
because it is vulnerable to degradation into ROS. Vesicle dopamine is the preferred form because it is protected from degradation and is available for signaling at the synapse.

3.2.2 Treatment State

Treatments for dopamine imbalances in the PD neuron include vitamin D (Puchacz et al., 1996) and edaravone (Xiong et al., 2011). These two treatments complement each other because vitamin D increases cytosolic dopamine levels by increasing expression of tyrosine hydroxylase, which is important in dopamine synthesis, while edaravone promotes VMAT expression,

**Figure 4: Vesicle Dopamine in PD** The decrease in cytosolic dopamine levels in the disease state is prevented in the treatment state, and the vesicle concentration becomes more constant.
increasing the ability of dopamine to be transported to the vesicles. The treatment state initially follows the disease state progression with a sharp increase in cytosolic dopamine levels and corresponding decrease in dopamine vesicle concentration, but then corrects to normal cytosolic dopamine levels (Fig. 3). Full treatment returns to normal levels much more quickly than delayed treatment does, and delayed treatment reaches the same maximum concentration difference as the disease state before declining. Only a slight decrease from baseline in vesicle dopamine concentration is observed with full treatment (Fig. 4). Delayed treatment allows for a much larger gap from the baseline that is never recovered within the scope of the model.

**Figure 5: Reactive Oxygen Species in PD** The level of reactive oxygen species is much lower in the treatment state than the disease state.
3.3 ROS and RNS

3.3.1 Disease State
Mitochondrial dysfunction, dopamine metabolism rate, ROS production rates, and RNS production rates are increased in the disease state while antioxidant concentrations are decreased to trigger ROS and RNS accumulation. The ROS and RNS portrayed in Figure 5 consist of the sums of the levels of cytosolic $O_2^-$, $H_2O_2$, $OH^-$, $ONOO^-$, NO, and mitochondrial $O_2^-$ in the neuron, as well as extracellular NO.

3.3.2 Treatment State
Antioxidant treatments included in the model are vitamin D, edaravone, and NAC (Samuni et al., 2013). Vitamin D can help to decrease cytosolic $O_2^-$ concentrations, and prevent $Ca^{2+}$ influx into the cell. $Ca^{2+}$ buildup in the mitochondria can cause excess $O_2^-$ production (Gandhi et al., 2009). Edaravone prevents mitochondrial DNA damage, reducing mitochondrial dysfunction (Xiong et al., 2011). NAC acts as an antioxidant in several ways. It is a precursor to glutathione, which is important in neutralizing $H_2O_2$. It can also react with $ONOO^-$ to degrade it into $NO_2^-$ and $OH^-$, and then react with those two species to form $HNO_2$ and water. Full treatment greatly reduced ROS and RNS presence in the neuron (Fig. 5). Delayed treatment originally follows the course of the disease state, but then begins to approach the full treatment state.

3.4 Tau Phosphorylation, Neurofibrillary Tangles, and Lewy Bodies

3.4.1 Disease State
Tau phosphorylation is triggered by increasing activated GSK-3β concentrations by decreasing insulin signaling, indirectly triggering p38 phosphorylation, and increasing α-synuclein
aggregations, which interact with tau and create toxic accumulations of the two proteins (Lei et al., 2010). Hyperphosphorylated tau in the disease state increases sharply compared to the baseline state (Fig. 6). Neurofibrillary tangles are a consequence of tau hyperphosphorylation and increase accordingly (Fig. 7). Lewy bodies are the result of aggregated α-synuclein, hyperphosphorylated tau, and other misfolded proteins, and increase in concentration as these species become more numerous (Fig. 8).

Figure 6: Phosphorylated Tau in PD Tau Phosphorylation is elevated in Parkinson’s disease, but is slowed in the treatment state.
3.4.2 Treatment State

Treatments included in the model that affect tau phosphorylation, neurofibrillar tangles, and Lewy bodies are lithium (Petit-Paitel et al., 2009), edaravone (Zhou et al., 2013), and sodium butyrate (Taylor et al., 2013). Lithium promotes GSK-3β phosphorylation, which prevents it from phosphorylating tau. Edaravone also inhibits tau phosphorylation. Sodium butyrate triggers the expression of MKP-1, which prevents tau phosphorylation by inhibiting p38 activation.

Phosphorylated tau is considerably diminished in the treatment state, but is still present (Fig. 6). Neurofibrillary tangles (Fig. 7) and Lewy bodies (Fig. 8) decline at a greater rate. In these three cases, a delayed treatment does cause a decrease in species concentration, but still continues the

![Figure 7: Neurofibrillary Tangles in PD](image)

Neurofibrillary tangles are increasingly present in the disease state, but are present at a lower level in the treatment state.
upward trend characteristic of the disease state. Delayed treatment slows the accumulation of these species but does not prevent it.

Figure 8: Lewy Bodies in PD Lewy body increase in Parkinson’s disease is lessened in the treatment state.

3.5 p38 Phosphorylation

3.5.1 Disease State

Decreasing the rate of insulin signaling, increasing the concentrations of ROS, and increasing the presence of prostaglandin J2 from the baseline state increases the activation of p38 in the disease state (Fig. 9). A decrease in the availability of parkin as an E3 ubiquitin ligase in the p38 degradation pathway is also a contributing factor to the excess p38 phosphorylation. As a result
of p38 phosphorylation, mitochondrial dysfunction, apoptosis, tau phosphorylation, dopamine synthesis, and Hsp27 activation also increase.

3.5.2 Treatment State

The full treatment state reduces p38 concentrations past the baseline state (Fig. 9). Activation of MKP-1 through sodium butyrate treatment inhibits p38 phosphorylation (Taylor et al., 2013). Sodium butyrate increases expression of the DUSP1 gene, increasing the expression of MKP-1. This phosphatase is responsible for dephosphorylating p38, rendering it inactive. The reduction in ROS levels also contributed to the decline of the p38 concentration, as they are less available

Figure 9: Phosphorylated p38 in PD The disease state includes increased phosphorylation of p38, which is attenuated in the treatment state.

3.5.2 Treatment State

The full treatment state reduces p38 concentrations past the baseline state (Fig. 9). Activation of MKP-1 through sodium butyrate treatment inhibits p38 phosphorylation (Taylor et al., 2013). Sodium butyrate increases expression of the DUSP1 gene, increasing the expression of MKP-1. This phosphatase is responsible for dephosphorylating p38, rendering it inactive. The reduction in ROS levels also contributed to the decline of the p38 concentration, as they are less available
to promote the phosphorylation. Delayed treatment failed to produce similar results. Instead, it predicted an increase in phosphorylated p38 compared to the baseline state, but still produced a positive impact by remaining at a lower concentration than in the disease state.

3.6 Cell Death

3.6.1 Disease State

Cell death can be triggered by apoptosome formation following activation of the caspase cascade by ROS in the cytosol, or by mitochondrial dysfunction and release of cytochrome c. Both cytosolic and mitochondrial ROS are elevated in the disease state. Lewy bodies and

Figure 10: Cell Death in PD The treatment state corrects for some of the cell death caused by pathways influenced by insulin signaling in Parkinson’s disease.
neurofibrillary tangles can also cause cell death. Finally, DNA fragmentation and chromosome condensation caused by AIF presence in the nucleus can lead to apoptosis. AIF is released along with cytochrome c as the PTP opens on the mitochondrial membrane. These factors all contribute to the increased probability of apoptosis seen as the model progresses (Fig. 10).

3.6.2 Treatment State

Apoptosis is prevented by several drugs including edaravone (Cheng et al., 2014; Xiong et al., 2011), Sodium butyrate (Taylor et al., 2013), cyclosporin A, and nortriptyline (Lamarche et al., 2012). Edaravone prevents apoptosis by inhibiting tau phosphorylation, promoting the expression of the mitochondrial protein Bcl-XL, and inhibiting the expression of the related Bax protein. The Bax protein binds to the truncated version of Bid and increases opening of the PTP. Bcl-XL can bind to the Bax/Bid complex to prevent this process. Sodium butyrate inhibits the apoptotic proteins Jun and p38 from being activated through its promotion of MKP-1 expression. Cyclosporin A and nortriptyline prevent the PTP from opening and releasing apoptotic factors such as cytochrome c, SMAC/DIABLO, and AIF. Cell death is successfully prevented if the treatment is presented at disease onset, but is still present, albeit in a diminished state, when the treatment is delayed.

4. AD Results

4.1 Insulin Signaling and Inflammation

4.1.1 Disease State

Insulin resistance (Fig. 11) was achieved by decreasing the rate at which insulin bound to its receptor and at which the receptor substrate was activated. The condition was further exacerbated
in the disease state with the onset of inflammation and the presence of Aβ oligomers, which compete with insulin for receptor interactions. Inflammation (Fig. 12) is triggered in the glia by the presence of ROS and the release of NF-kB from its inhibitor, allowing it to enter the nucleus and begin its actions as a transcription factor for pro-inflammatory cytokines and enzymes that produce even more ROS.

4.1.2 Treatment State

![Insulin Signaling](image)

**Figure 11: Insulin Signaling in AD** Progressive insulin signaling accompanying AD is attenuated with insulin sensitizing treatment
Insulin sensitization (Fig. 11) is achieved in this model by the inclusion of pioglitazone and sodium butyrate, which increase interactions between insulin and its receptor (Gao et al., 2009; Heneka et al., 2005). Pioglitazone and sodium butyrate are successful in recovering normal insulin signaling in both a full treatment scenario and recover almost all signaling in the delayed treatment model, although because the signaling had already been further decreased, it acted more slowly than the full treatment. This model does not include a treatment for inflammation directly, and once NF-κB has been activated by ROS, the presence of antioxidants, which the model does include, will not necessarily stop inflammation triggered by the newly expressed pro-

![Figure 12: Inflammation in AD](image)

Inflammatory processes in AD increase as the disease progresses
inflammatory cytokines. The inflammation does decrease slightly from the reduction of ROS (Fig. 12).

4.2 ROS and Mitochondrial Dysfunction

4.2.1 Disease State

The concentration of ROS in the model was determined by summing the concentrations of all ROS in the neuron, astrocyte, and microglia and include O$_2^-$, H$_2$O$_2$, OH-, NO, and ONOO-. In the disease model, the ROS steadily increase during the progression of the disease state (Fig. 13). ROS contribute to cell damage by reacting with lipids, proteins, and DNA and altering or

![Reactive Oxygen Species Total](image)

**Figure 13: Reactive Oxygen Species in AD** O$_2^-$, H$_2$O$_2$, OH-, and ONOO- in neurons, astrocytes, and microglia all increase with AD
preventing their function. Mitochondria are especially vulnerable to ROS toxicity because respiration is a major source of ROS in the cell. Mitochondrial dysfunction data shown (Fig. 14) includes both complex I dysfunction and mitochondrial membrane depolarization, which both interfere with normal respiratory function and contribute to further production of ROS. In the model, mitochondrial dysfunction increases at an increasing rate over the course of AD.

4.2.2 Treatment State

The treatment strategy for mitochondrial dysfunction focused on preventing ROS buildup. The antioxidant curcumin was chosen for this model. Curcumin is a naturally occurring substance

![Figure 14: Mitochondrial Dysfunction in AD](image)

**Figure 14: Mitochondrial Dysfunction in AD** Complex I dysfunction and mitochondrial membrane depolarization can both be prevented by the neutralization of reactive oxygen
that is present in the spice turmeric, and is responsible for its characteristic yellow color. Curcumin is able to neutralize two ROS per molecule by donating H+ to the ROS, rendering them less reactive (Barzegar 2012). The curcumin is able to reduce the amounts of ROS in the system, but not completely erase their presence (Fig. 13). Interestingly, delayed treatment is able to quickly reduce ROS concentrations to full treatment levels. This does not, however, transfer to mitochondrial dysfunction (Fig. 14). Almost all mitochondrial dysfunction is able to be attenuated by the presence of an antioxidant if it is administered at the onset of the functional

Figure 15: Ca²⁺ Dysregulation in AD Ca²⁺ increases in toxic amounts in Alzheimer’s disease, which can be prevented by inhibition of Ca²⁺ entering the cell from the extracellular environment
deterioration. If it is administered after some dysfunction has already occurred, however, it can
delay but not prevent further respiratory inhibition.

4.3 Ca\textsuperscript{2+} Dysregulation

4.3.1 Disease State

Ca\textsuperscript{2+} influx can occur from two sources in the model: entry into the cell from ion channels and
release of Ca\textsuperscript{2+} stores in the endoplasmic reticulum in response to stressors. Both of these
processes are activated in AD with the result that the intracellular Ca\textsuperscript{2+} concentration increases
during the disease state (Fig. 15), leading to abnormal Ca\textsuperscript{2+} signaling that contributes further to
disease progression.

4.3.1 Treatment State

The treatment state focused on preventing Ca\textsuperscript{2+} influx from ion channels, not preventing
endoplasmic reticulum Ca\textsuperscript{2+} release. The channel blocker MRS2481 is included in the model to
this effect (Diaz et al., 2009). If added before any abnormal Ca\textsuperscript{2+} signaling, the inhibitor
effectively prevents an overabundance of Ca\textsuperscript{2+} in the cytosol (Fig. 15). If Ca\textsuperscript{2+} has already started
to accumulate, however, the treatment can only partially block further dysregulation. This
additional Ca\textsuperscript{2+} may derive from the endoplasmic reticulum, as too much cytosolic Ca\textsuperscript{2+} can
cause the endoplasmic reticulum to release its Ca\textsuperscript{2+} stores, further exacerbating the aberrant
signaling (Casley et al., 2009).
4.4 Neurofibrillary Tangles

4.4.1 Disease State

Neurofibrillary tangles are increased in the Ad model compared to the baseline in several ways. The increased insulin resistance prevents a kinase cascade that blocks GSK-3β, which can phosphorylate tau. Additionally, Ca\(^{2+}\) increases activate calpain to further increase tau hyperphosphorylation. Finally, ROS can cause inflammation and p38 activation, both of which can contribute to tau hyperphosphorylation. These hyperphosphorylated tau are then able to

**Figure 16: Neurofibrillary Tangles in AD** Neurofibrillary tangles increase during AD, but can be prevented primarily by inhibiting tau phosphorylation
accumulate in neurofibrillary tangles, which are present in increasing amounts in the AD model (Fig. 16).

4.4.2 Treatment State

The treatment state includes several methods of reducing neurofibrillary tangle production. Curcumin as an antioxidant prevents some inflammation and p38 phosphorylation. Pioglitazone can inhibit GSK-3β activity by increasing insulin signaling. MRS2481 reduces calpain activation by reducing Ca²⁺ signaling. With the final addition of a direct GSK-3β inhibitor, lithium chloride (Noble et al., 2005), neurofibrillary tangles are dramatically decreased in the full treatment

Figure 17: Beta Secretase in AD Increases in beta secretase concentrations are corrected in the treatment state
model (Fig. 16). In the delayed treatment state, the neurofibrillary tangle formation process can only be partially corrected.

4.5 β-secretase and Aβ Oligomers

4.5.1 Disease State

β-secretase is increased in the model (Fig. 17) through the increase in inflammation and indirectly by Ca$^{2+}$ signaling from an increase in calpain. Accordingly, Aβ oligomers are increased (Fig. 18) through the increased production of Aβ from β-secretase increase, amplified

![Graph showing relative concentration difference of cytosolic Aβ oligomers over time](image)

**Figure 18: Amyloid Beta Oligomers in AD** Amyloid beta oligomers are greatly reduced in the treatment state compared to the disease state.
APP expression from glial IL-1β signaling as a result of inflammatory signaling, and greater GSK-3β activity from a lack of insulin signaling.

4.5.2 Treatment State

β-secretase is treated in the model through pioglitazone, which acts as a β-secretase inhibitor as well as an insulin sensitizer (Heneka et al., 2005). This treatment decreases β-secretase to near normal levels after an initial rise in concentration in the full treatment state (Fig. 17), and provides some inhibitory behavior, although to a lesser extent, in the delayed treatment model. Aβ oligomers sharply decrease in the full treatment state (Fig. 18). This is a result of a lack of Aβ

![Phosphorylated p38](image)

**Figure 19: p38 Phosphorylation in AD** p38 is increasingly phosphorylated as AD progresses, but can be inhibited in the treatment state.
availability because of β-secretase scarcity, as well as inflammation decreases from curcumin’s antioxidant properties and recovered insulin signaling from pioglitazone sensitization. Curcumin also more directly inhibits Aβ aggregation (Ganugapati et al., 2015) by interacting with the active site of the APP. In the delayed treatment state, the oligomers also decrease below disease levels, but not to the extent of the full treatment.

4.6 Phosphorylated p38 and Cell Death

4.6.1 Disease State

![Figure 20: Cell Death in AD](image)

Cell death increases throughout disease progression, but is somewhat attenuated in the treatment state.
p38 increases decidedly as the disease state advances (Fig. 19). This is a result of an increased number of ROS and inflammation accompanied by a decrease in insulin signaling. p83 activation triggers cell death in several ways, contributing to the increase in degeneration in the disease state (Fig. 20). Endoplasmic reticulum stress from abnormal cytosolic Ca2+ accumulation, lysosome permeability, and ROS more directly also contribute to the increasing likelihood that a neuron will die.

4.6.2 Treatment State

While p38 activation initially increases even during the full treatment state, it begins decreasing about halfway through the model (Fig. 19). The delayed treatment state also includes a decrease in p38 phosphorylation, but to a lesser extent. Curcumin as an antioxidant and pioglitazone as an insulin sensitizer help to prevent p38 activation, and an additional p38 inhibitor, sodium butyrate, is also included in the model (Taylor et al., 2013). Cell death is affected by every process previously discussed, and therefore every treatment included in the model works to ultimately prevent degeneration. This effort is somewhat successful, as the full treatment state decreases cell death, and improves slightly in efficacy as the model progresses (Fig. 20). The delayed treatment, however, is much less effective.

5. Discussion

5.1 PD

5.1.1 Disease State

The disease state model mimics the current understanding of PD in that it shows increases in inflammation, apoptotic factors, ROS and RNS, abnormal dopamine concentrations, and elevated
levels of phosphorylated tau, neurofibrillary tangles, and Lewy bodies, which are characteristic of PD. These factors are only a fraction of the numerous of processes that typify PD, which also include but are not limited to the misfolding of α-synuclein, gene mutations, endoplasmic reticulum stress, and ubiquitin proteasome system malfunction, which are not fully explored in this model. The disease state modeled here is exacerbated by a loss of insulin signaling, usually caused by an excess of fats and sugars in the diet and a major factor in the development of T2DM. The model also suggests that dopaminergic neuronal insulin signaling is highly impaired in PD. This is likely caused by PD effects such as chronic inflammation and oxidative stress, which are common causes of insulin resistance in T2DM patients (Evans et al., 2002).

5.1.2 Treatment State

The model suggests a variety of treatment options to ameliorate both causes and symptoms of PD. Vitamin D, Li, aspirin, NAC, edaravone, pioglitazone, Sodium butyrate, cyclosporin A, and nortriptyline are the treatments included in the version of the model presented in this paper. Vitamin D acts as a ROS scavenger as well as decreasing inflammation. Lithium is a GSK 3β inhibitor. It is currently used as a treatment for bipolar disorder, but is being researched as a treatment for PD. Aspirin, a common, over-the-counter pain medication, is a NSAID and inhibits the inflammatory cytokine COX2. NAC acts as both an anti-inflammatory and antioxidant compound by inhibiting NF-κB, increasing glutathione concentrations, and reacting to neutralize ROS and RNS (Model 13). NAC is currently used as a treatment for a variety of psychiatric conditions including schizophrenia, obsessive-compulsive disorder, and addiction (Dean et al., 2011). Edaravone protects against mitochondrial damage and tau phosphorylation, while promoting dopamine entry into vesicles. It is currently being investigated as a PD medication, as
well as being involved in ongoing clinical trials to evaluate its potential as a treatment for ALS, another neurodegenerative disease. Pioglitazone is a known insulin sensitizer and is used in the treatment of T2DM. Sodium butyrate prevents apoptosis by inhibiting the activation of pro-apoptotic proteins p38 and Jun. It also acts as an insulin sensitizer, and is currently being studied as a treatment for T2DM and the neurodegenerative condition Huntington’s disease. Cyclosporin A, an immunosuppressant, and nortriptyline, an antidepressant, both block apoptosis by preventing the PTP from opening.

PD symptoms occur only after the disease progression is well under way. Treatment, therefore, is often delayed. This model includes one condition in which treatment is introduced at the onset of the disease, and one in which treatment is introduced halfway through the modeled disease progression. The differences between the scenarios highlight the importance of early detection of PD and, for the familial version of the disease, the introduction of possible preventative measures. The delayed treatment states for insulin resistance (Fig. 1), cell death (Fig. 10), p38 phosphorylation (Fig. 9), Lewy bodies (Fig. 8), neurofibrillary tangles (Fig. 7), and tau

Model 13: Example of treatment action—NAC as an antioxidant and NF-κB inhibitor in PD
phosphorylation (Fig. 6) each resemble their disease state simulations more than their full treatment states. ROS (Fig. 5) and inflammation (Fig. 2) levels are partially corrected, but still high. Cytosolic dopamine (Fig. 3) levels eventually return to normal, and while vesicle dopamine (Fig. 4) levels are stabilized with treatment, the original concentration was not restored.

5.2 AD

5.2.1 Disease State

The disease state accurately accounts for many of the pathological trends observed in AD brains, including increases in inflammation, cytosolic Ca\(^{2+}\), ROS and mitochondrial dysfunction, neurofibrillary tangles, Aβ oligomers, and cell death. Insulin resistance is connected to all of these changes and is a well characterized aspect of AD. Insulin signaling, or a lack thereof, affects the two main downstream components of AD, neurofibrillary tangles and Aβ oligomers, both of which are composed of pathologically modified proteins or peptide fragments. Both T2DM and T1DM effects, insulin receptor desensitization and a lack of insulin, are observed in AD conditions, further linking neurodegeneration to metabolic defects.

5.2.2 Treatment State

The approach to the AD treatment state was somewhat different than in the PD model. The PD model was more concerned with suggesting pathways to treat rather than specific compounds to treat them, although specific compounds were suggested. The AD model suggests five treatments instead of ten, representing a more realistic, although still complicated, drug cocktail. The AD treatments were chosen in many cases on their ability to affect multiple implicated pathways, allowing for a reduction in total treatments included. This approach minimizes the likelihood of
severe side effects and drug interactions. These aspects were not investigated in the model, however, because the focus is on the pathways themselves, not specific treatments. If two of the treatments suggested happen to interact with each other, for instance, other compounds can be found that inhibit the same processes.

This model included several treatments for AD that overlap with PD treatment suggestions. Sodium butyrate is able to sensitize the insulin receptor as well as prevent p38 activation, which are important processes that require intervention in both models. Lithium also acts more downstream of the insulin receptor to reduce tau hyperphosphorylation in both models. Pioglitazone was incorporated in the PD model as an insulin sensitizer only, but also acts as a β-secretase inhibitor in the AD model. The molecule MRS2481 is a Ca²⁺ channel blocker and prevents an influx of Ca²⁺. Curcumin is a potent naturally occurring antioxidant molecule that is currently being investigated as a treatment for AD. Not only does it neutralize ROS, but it also prevents Aβ oligomerization by binding to the Aβ active site. Taken together, these treatments all contribute to the rectification of the multiple biochemical pathways affected by insulin resistance in AD.

5.3 MATLAB

This paper introduces a new protocol for coding neurodegenerative systems using MATLAB instead of PLAS. Unlike PLAS, MATLAB is capable of analyzing all aspects of the quantitative model, from solving the ODEs to preparing graphs. PLAS requires the use of separate programs such as Microsoft Excel for any data analysis and visualization required after the ODEs are solved. MATLAB is also able to take into account multiple qualitative outcome possibilities for
a single species. In other words, MATLAB is able to recognize a condition, such as a species reaching a threshold concentration, and substitute the original equation with an alternate one leading to a qualitatively different outcome once the species reaches the threshold. Another advantage of MATLAB is the ability to order the solutions to the equations so that the species most sensitive to the change are immediately apparent. Finally, MATLAB can introduce new events, such as introducing or altering treatment dosages, at any time during the simulation. PLAS is only able to use the initial values given at the onset of the simulation. Overall, MATLAB is the more flexible and efficient analytical tool.

6. Conclusion

The two models described in this paper explore the reciprocal intensification of PD and insulin resistance and AD and insulin resistance through a mathematical lens. They provide a quick, cost-effective means of evaluating possible neurodegenerative disease treatment options for patients who also exhibit insulin resistance, and suggests mechanisms for the interactions between the conditions. The PD model emphasizes dopaminergic neuron deterioration through ROS production via dysfunctional mitochondria and dopamine metabolism as well as Lewy body and neurofibrillary tangle production through hyperphosphorylated tau accumulation. The model also simulates the reduction in insulin signaling that occurs as a result of the chronic inflammation and ROS production that can accompany PD. Insulin signaling is partially lost even when it is not initially impaired. The AD model focuses on insulin signaling impairment through inflammatory processes, including ROS production and accompanying mitochondrial production, as well as Ca2+ dysregulation, the characteristic AD pathological components neurofibrillary tangles and Aβ oligomers, and lastly p38 phosphorylation and cell death. .
Finally, the models evaluate the neuroprotective ability of a variety of treatments, both experimental and currently available to treat PD, AD, or T2DM. The models predict that a combined approach, initiated as early as possible and targeting a wide range of pathways, is the most effective.

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The qualitative models were developed using the program CellDesigner version 4.3, and can be found at http://www.celldesigner.org/.

The mathematical models were developed using MATLAB R2014a, which could be found at the following website upon beginning this work: http://www.mathworks.com/products/matlab/.

**Abbreviations:**
BST, Biochemical Systems Theory; PLAS, Power Law Analysis and Simulation; PD, Parkinson’s Disease; T2DM, Type-II Diabetes Mellitus; T1DM, Type-I Diabetes Mellitus; CNS, Central Nervous System; ROS, Reactive Oxygen Species; RNS, Reactive Nitrogen Species; AD, Alzheimer’s disease; Aβ, Amyloid Beta; APP, Amyloid Precursor Protein; ODE, Ordinary Differential Equation; PPARγ, Peroxisome-Proliferator-Activated Receptor γ; IL-6, Interleukin-6; IL-1β, Interleukin-1β; TNFα, Tumor Necrosis Factor α; M-CSF, Macrophage Colony-Stimulating Factor; COX2, Cyclooxygenase 2; NO, Nitric Oxide; H₂O₂, Hydrogen Peroxide; O₂⁻, Superoxide Radical; OH⁻, Hydroxyl Radical; ONOO⁻, Peroxynitrite; HNO₂, Nitrous Acid; NF-kB, Nuclear Factor κB; VMAT, Vesicular Monoamine Transporter Proteins; SOD2, Superoxide Dismutase 2; PI3K, Phosphatidylinositol 3 Kinase; PIP2, Phosphatidylinositol Bisphosphate; PIP3, Phosphatidylinositol Trisphosphate; GSK-3β, Glycogen Synthase Kinase 3β; MKP-1, Mitogen-Activated Protein Kinase Phosphatase 1; MCP1, Dual Specificity Protein Phosphatase 1; PTP, Permeability Transition Pore; AIF, Apoptosis-Inducing Factor; SMAC/DIABLO, Second Mitochondria-Derived Activator of Caspases/Direct IAP Binding Protein with Low pI; IAP, Inhibitor of Apoptosis; NAC, N-acetylcysteine; NOS, Nitric Oxide Synthase; NSAID, Non-Steroidal Anti-inflammatory Drug; ALS, Amyotrophic Lateral Sclerosis
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