Mathematical Modeling for the Pathogenesis of Alzheimer’s Disease

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Abstract

Despite extensive research, the pathogenesis of neurodegenerative Alzheimer’s disease (AD) still eludes our comprehension. This is largely due to complex and dynamic cross-talks that occur among multiple cell types throughout the aging process. We present a mathematical model that helps define critical components of AD pathogenesis based on differential rate equations that represent the known cross-talks involving microglia, astroglia, neurons, and amyloid-β (Aβ). We demonstrate that the inflammatory activation of microglia serves as a key node for progressive neurodegeneration. Our analysis reveals that targeting microglia may hold potential promise in the prevention and treatment of AD.

Introduction

Alzheimer’s disease (AD) is one of the most prevalent neurodegenerative disorders associated with aging, causing dementia and related severe public health concerns [1]. Despite extensive research effort and progress, the pathogenesis of AD remains incompletely understood, partly due to highly complex and intertwined intercellular cross-talks taking place throughout the aging process [2]. Consequently, despite limited treatment options to manage and slow the progression of AD, no effective cure is available.

Although the deposition of amyloid-β (Aβ) peptides and formation of senile plaques in the brain is the cardinal morphological feature identifying the clinical phenotype of AD [3,4], increasing clinical and basic studies suggest that inflammatory activation of microglia may play an equally important role during the initiation and progression of the disease [5]. Microglia are resident innate immune macrophages within brain tissues, capable of expressing pro-inflammatory mediators and reactive oxygen species when activated by inflammatory signals including amyloid-β (Aβ) [6]. In healthy brains, together with quiescent astroglia (Aq), resting microglia may adopt an anti-inflammatory state (M2) and in turn foster neuron survival (Ns) and prevent astroglia proliferation (Ap) [7,8]. As inflammatory signals (e.g. Aβ) gradually build, microglia may adopt an activated pro-inflammatory state (M1), leading to Aq proliferation and neuron death (Nd) [9,10,11]. Neuronal debris, amyloid-β (Aβ), and/or proliferating astroglia (Ap) may in turn further exacerbate the inflammatory phenotype of M1 macroglia [12,13]. The multiple positive and negative feedbacks among these cells are thus crucial for neurodegeneration that eventually alters the neuronal structure and function during the pathogenesis of AD (Figure 1).

Due to its multi-cellular components and complex nature, conventional experimental approaches have failed to identify critical underlying causes for AD, contributing to the lack of an effective therapeutic treatment. Mathematical models can serve as powerful tools to understand the molecular and cellular processes that control complex diseases [14,15]. Indeed, there have been several attempts to model the process of senile plaque formation [16,17,18,19]. Specifically, these approaches focused on a nucleation step that is coupled with rates for the irreversible binding of Aβ monomers to the fibril ends, the lateral aggregation of filaments into fibrils, and fibril elongation through end-to-end association. Other modeling efforts examined the signaling cascade responsible for microglia migration and activation in response to an initial inflammation-provoking stimulus involving Aβ [16,20].

However, no systematic modeling approaches have been reported to examine the network cross-talks among microglia, neuron, and astroglia, and the corresponding pathological consequence. Here, we evaluate the dynamic network involving multiple cross-talks among distinct states of microglia, astroglia, and neurons through a mathematical model. Our approach has led to an intriguing insight suggesting that microglia activation in addition to a threshold for Aβ may be the critical initiator for the pathogenesis of AD.

Methods

Mathematical Method

We propose a sixteen pathway AD mechanism involving seven species that is shown schematically in Fig. 1. The paths have rates  that implicitly represent the influences of intercellular signaling along them. The mechanism is based on an assumption of constant risk of neuronal death, i.e., a single event randomly initiates cell death independently of the state of any other neuron at any instant [21]. The spatiotemporal influence of diffusion is
neglected since local cell events are assumed to occur on a slower timescale than signal dispersion through chemotaxis.

The seven rate equations for the cell populations and the number of Aβ molecules in an arbitrary local volume can be written through seven coupled rate equations, namely,

\[
\frac{dN_s}{dt} = x_1 A_q - x_2 A_p - x_3 M_1, \tag{1}
\]

\[
\frac{dN_d}{dt} = -dN_s/dt, \tag{2}
\]

\[
\frac{dA_q}{dt} = x_4 M_2 - x_5 M_1, \tag{3}
\]

The values of the sensitivity coefficients \(S(N_j, j = s, d) = dN_j/dX(0)\) determined after 20 years for tenfold perturbations, i.e., \(10 \times 10^{-i}, i\) in these initial values.

d\(\frac{dA_p}{dt} = -dA_p/dt, \tag{4}\)

d\(\frac{dM_2}{dt} = (x_6 + x_11) N_s - x_{10} N_d + (x_7 + x_{12}) A_q - 20 M_1 + x_{14} M_2 - (x_{18} + x_{13}) A\beta, \tag{5}\)

d\(\frac{dM_1}{dt} = -dM_2/dt, \tag{6}\)

d\(\frac{dA\beta}{dt} = x_{15} N_s - x_{16} M_2. \tag{7}\)

These relate the change in each cell population or the number of Aβ molecules at any instant to the values of all species at that instant.

**Table 1. Mathematical parameters describing the functional interactions among various cell types.**

| Rate | 1/year | Pathway | \(S(N_s)\) | \(S(N_d)\) | \(S(M_1)\) | \(S(M_2)\) | Sensitivity |
|------|--------|---------|-----------|-----------|-----------|-----------|-------------|
| \(\tau_1\) | 10^{-5} | \(N_s \rightarrow N_s\) | 50000 | -50000 | -6000 | 6000 | Strong |
| \(\tau_2\) | 10^{-3} | \(N_s \rightarrow N_d\) | -500 | 500 | 60 | 60 | Weak |
| \(\tau_3\) | 10^{-2} | \(M_1 \rightarrow N_d\) | -200 | 200 | 35 | 35 | Weak |
| \(\tau_4\) | 10^{-4} | \(M_2 \rightarrow A_q\) | 500 | -500 | 150 | -150 | Weak |
| \(\tau_5\) | 10^{-2} | \(M_1 \rightarrow A_p\) | -3 | 3 | 1 | -1 | Weak |
| \(\tau_6\) | 10^{-2} | \(N_s \rightarrow M_1\) | 500 | -500 | -6000 | 6000 | Weak |
| \(\tau_7\) | 10^{-4} | \(A_q \rightarrow M_2\) | 5000 | -5000 | -50000 | 50000 | Strong |
| \(\tau_8\) | 10^{-2} | \(A\beta \rightarrow M_2\) | -400 | 400 | 5000 | -5000 | Moderate |
| \(\tau_9\) | 10^{-2} | \(M_1 \rightarrow M_2\) | -30 | 30 | 250 | -250 | Weak |
| \(\tau_{10}\) | 10^{-2} | \(N_d \rightarrow M_1\) | -8 | 8 | 90 | -90 | Weak |
| \(\tau_{11}\) | 10^{-2} | \(N_d \rightarrow M_2\) | 500 | -500 | 6000 | 6000 | Moderate |
| \(\tau_{12}\) | 10^{-4} | \(A_q \rightarrow M_1\) | 5000 | -5000 | -5000 | 50000 | Strong |
| \(\tau_{13}\) | 10^{-2} | \(A\beta \rightarrow M_1\) | -400 | 400 | 5000 | -5000 | Moderate |
| \(\tau_{14}\) | 10^{-4} | \(M_1 \rightarrow M_2\) | 5000 | -5000 | -5000 | 50000 | Strong |
| \(\tau_{15}\) | 1 | \(N_s \rightarrow A\beta\) | -10 | 10 | 100 | -100 | Weak |
| \(\tau_{16}\) | 10^{-2} | \(M_2 \rightarrow A\beta\) | 100 | -100 | -1000 | 1000 | Weak |
| \(\tau_e\) | 1 | \(M_2 \rightarrow A\beta\) | 8 | -8 | -100 | 100 | Weak |

The values for the sensitivity coefficients \(S(N_j, j = s, d) = dN_j/dX(0)\) are determined after 20 years for \(\pm 2.5\%\) perturbations in each \(x_i\) value. A cell population is more sensitive to a change in a rate that produces a larger value of \(|S(N_j)|\). Positive \(S(N_j)\) imply that a rate contributes to an increase in \(N_j\) while a negative value entails a corresponding population decrease.
For instance, Eq. (1) relates the rate of change in Ns to the Aq, Ap, and M1 populations with the pathway weights \( a_1 \), \( a_2 \), and \( a_3 \), respectively. Whereas Aq increases the rate of change of Ns, Ap and M1 decrease it. Equation (5) for the rate of change of the M2 population is the most complex, since it involves nine pathway weights, and five cell populations and Aβ. The conversion of Ns into Nd is irreversible, whereas those of Aq and M2 into Ap and M1 are reversible.

The rates for each \( a_i \) are specified, as shown in presented in Table 1 for each pathway. Since the literature points to the path Ns \( \rightarrow \) Aβ being dominant, we assume that it is also the fastest. Its rate is set at 1/year, i.e., each year every Ns cell stimulates the formation of a sustaining an Aβ molecule. Likewise, since neuronal survival decreases significantly once disease progresses, we assume that the overall path M2 \( \rightarrow \) M1 \( \rightarrow \) Ns is slow so that the associated rates \( a_1 \) and \( a_4 \) are also relatively the smallest. The other rates are similarly specified in terms of their relative abilities to facilitate or inhibit the formation of a cell or Aβ molecule according to the particular pathway. Next, we specify the initial composition of the volume under consideration. These initial conditions for the seven species are presented in Table 2.

**Results**

Our objective is to be able to describe neuropathogenesis during AD in terms of the Ns and Nd populations. Hence, we first determine the sensitivities of these cells to changes in the rates \( a_i \), using the usual definition of the sensitivity coefficient,

\[
S(N_j) = \frac{dN_j}{dx_j}, j = s, d.
\]  

The sensitivity coefficients for Ns, Nd, M1, and M2 cells, presented in Table 1, are determined after 20 years for \( \pm 2.5\% \) perturbations in each \( a_i \) value. A cell population is more sensitive...
to a change in a rate that produces a larger value of \(|S(N_j)|\). Positive values for \(S(N_j)\) imply that a rate contributes to an increase in \(N_j\) while a negative value implies that its influence leads to a corresponding population decrease. The sensitivity analysis shows that the \(N_3\) and \(N_4\) populations are most sensitive to the path \(A_{13} \rightarrow N_3\), which increases neuronal survival and decreases neuron death. Important paths that inhibit neuropathogenesis include \(A_{13} \rightarrow M_2\), \(A_1 \perp M_1\) and \(M_2 \perp M_1\), while those that enhance disease involve \(M_1 \rightarrow N_3\), \(A_B \perp M_2\) and \(A_B \rightarrow M_1\).

A similar analysis that perturbs the initial cell populations and the number of \(A_B\) molecules tenfold is presented in Table 2. It shows that, in comparison to the other species, the \(M_1\) population is most sensitive to these substantial perturbations in the initial amount of any species while \(N_3\) is only sensitive to the initial amounts of \(M_1\) and \(M_2\). This implies an important role for microglia during AD progression. The sensitivity coefficients \(S(M_1)\) and \(S(M_2)\), also presented in Table 1, show that, as for \(N_1\) and \(N_6\), the dominant paths that inhibit neuropathogenesis by affirming \(M_2\) and decreasing \(M_1\) are also \(A_{13} \rightarrow M_2\), \(A_{13} \perp M_1\) and \(M_2 \perp M_1\). Once again, paths 7 and 14 involving \(A_B\), i.e., \(A_B \perp M_1\) and \(A_B \rightarrow M_1\) promote AD progression. The model suggests that interventions aimed at decreasing \(\tau_{13}\) and \(\tau_{13}\), which involve \(M_1\), \(M_2\) and \(A_B\) and contribute to AD progression, are the ones more likely to diminish neuropathogenesis. This intuitive result emphasizes that decreasing the number of reactive microglia and ensuring a sufficient population of quiescent astroglia is important in treating AD.

The temporal variation in various species for the rates in Table 1 is illustrated in Fig. 2. Figure 2(a) presents the \(N_3\), \(M_1\) and \(A_B\) populations over 20 years, and Fig. 2(b) the corresponding values for \(N_3\) and \(A_B\). Most notable is the influence of the removal rate \(\tau_B\), which stabilizes the number of \(A_B\) molecules after three years. Following that period, there is only a gradual increase in \(N_3\) that is coupled with a corresponding decline in \(N_3\). Consequently, the microglia populations are also relatively stable. Therefore, the rates in Table 1 should be considered as being representative of a healthy population.

We examine the influence of varying \(\tau_B\) on neuropathogenesis in Fig. 3, which presents the \(M_1\), \(A_B\) and \(N_4\) populations over 20 years for three values of \(\tau_B\). As \(\tau_B\) decreases, there is an increasing neuronal death. Thus, all four populations, which are associated with AD progression, increase. While microglia play an important role in AD, Fig. 3 shows how the local \(A_B\) concentration plays a critical role in initiating and promoting AD.

We investigate this further by varying \(\tau_0\) and \(\tau_{13}\). Figure 4 presents results for the \(M_1\), \(N_4\) and \(A_B\) populations over 20 years for three values of \(\tau_{13}\). As \(\tau_{13}\) increases, the \(M_1\), \(A_B\) and \(N_4\) populations also increase, leading to an associated decrease in neuronal survival, as illustrated through Eqs. (1) and (2) of the mathematical model. A tenfold increase in \(\tau_{13}\) leads to a near doubling in \(N_4\) after 20 years. As \(N_4\) decreases so does \(A_B\), but the smaller protein concentration is still sufficient to promote neuropathogenesis among the smaller \(N_1\) population. Identical results are obtained for similar variations in the rate \(\tau_0\) for \(A_B \perp M_2\), since the sensitivity coefficients for each of \(M_1\) and \(N_4\) towards paths 8 and 13 are identical.

**Discussion**

We present a mathematical model for neuropathogenesis during AD that involves neurons, normal and reactive glial cells, and \(A_B\). It uses neuronal death as a surrogate for senile plaque formation. By monitoring neuronal health, we are able to identify intuitive strategies for interventions. In particular, the model suggests that the most effective intervention is one that improves the inhibition of reactive microglia and \(A_B\) by normal microglia, and ensuring a sufficient population of quiescent astroglia. Overall, neuropathogenesis proceeds through the production of reactive microglia.

Our analysis is consistent with experimental data that indicate that inflammation may be an early initiator for AD, long before the apparent senile plaque formation [22,23]. It further reinforces...
the notion that additional studies should be directed at examining earlier inflammatory signals and alterations involving microglia as a key node so as to better define AD initiation and understand mechanisms for effective prevention and treatment of the disease.

We realize that our mathematical analysis is an initial attempt to examine AD and may not fully account for the associate intertwined cellular communication pathways. Nevertheless, it serves as a hypothesis provoking and building process that should encourage integrated analyses of AD pathogenesis. Future experimental data examining the cross-talks among microglia, astroglia, and neurons will allow us to better refine our model and implement realistic parameters in the rate equations.

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