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Oxidant Antioxidant Balance in β-Cells Predicting Insulin Secretion Impairment under POP Exposure

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Abstract

Diabetes mellitus, a leading global health concern, is characterized by impaired insulin secretion and β-cell dysfunction. Oxidative stress, driven by an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, plays a significant role in this dysfunction. Persistent organic pollutants (POPs) such as PCB-153 and p,p'-DDE, which bioaccumulate in human tissues, have been identified as environmental agents that exacerbate oxidative stress, contributing to β-cell failure and the progression of diabetes. This study presents a mathematical model that simulates the interactions between ROS production, antioxidant depletion, and insulin secretion in pancreatic β-cells under varying levels of POP exposure. The model incorporates the dynamics of key antioxidants like glutathione (GSH) and catalase, and simulates the effects of antioxidant therapies such as N-acetyl-L-cysteine (NAC). Simulation results reveal that both low and high levels of POP exposure lead to significant ROS accumulation, GSH depletion, and reduced insulin secretion. Importantly, NAC treatment mitigates oxidative stress, restoring insulin secretion and delaying GSH depletion. The model highlights the critical role of antioxidants in protecting β-cells from oxidative damage and offers a predictive framework for assessing the long-term impacts of environmental pollutants on diabetes risk. These findings underscore the therapeutic potential of antioxidant treatments and the need for environmental pollutant regulation to reduce diabetes prevalence.

Keywords: Diabetes, β-cell dysfunction, oxidative stress, persistent organic pollutants, reactive oxygen species, insulin secretion, glutathione, antioxidant therapy, mathematical modeling, N-acetyl-L-cysteine.

Introduction

A. Background on Diabetes and β-Cell Dysfunction

Diabetes mellitus is a global health concern characterized by chronic hyperglycemia, with substantial implications for human health and the economy. It is generally classified into two primary types: Type 1 diabetes (T1D), where autoimmune destruction of pancreatic β-cells leads to an absolute insulin deficiency, and Type 2 diabetes (T2D), which involves a combination of insulin resistance and β-cell dysfunction. While T1D is primarily driven by immune system-mediated β-cell destruction, T2D arises from a failure of β-cells to compensate for the increasing insulin demands of insulin-resistant tissues [1], [2]. β-cell dysfunction plays a central role in both forms of diabetes and remains a critical point for therapeutic interventions [3].The mechanisms underlying β-cell dysfunction include genetic, epigenetic, and environmental factors, with oxidative stress emerging as a key contributor to β-cell failure. Oxidative stress results from an imbalance between the generation of reactive oxygen species (ROS) and the cell's capacity to detoxify them. In β-cells, oxidative stress can impair insulin production and secretion, a process fundamental for glucose regulation. Recent literature emphasizes the vulnerability of β-cells to oxidative stress, due in part to their relatively low antioxidant defenses compared to other tissues [4].

B. Persistent Organic Pollutants and their Role as Diabetogenic Agents

Persistent organic pollutants (POPs) are environmental contaminants with high stability, long-term persistence, and a tendency to bioaccumulate in the food chain and human tissues. Examples of these compounds include polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT) derivatives like p,p'-DDE, and dioxins such as TCDD. POPs have been widely studied for their endocrine-disrupting properties, and emerging evidence links them to metabolic diseases, including diabetes. POPs are known to exert toxic effects on pancreatic β-cells through the induction of oxidative stress, which disrupts normal insulin synthesis and secretion [5], [6]. The diabetogenic potential of POPs has been increasingly recognized, with several studies demonstrating that POP exposure promotes insulin resistance, β-cell dysfunction, and the onset of T2D . Epidemiological studies, such as those by Lee et al. (2010), have shown a correlation between serum concentrations of POPs and the incidence of T2D, particularly in populations with high levels of

bioaccumulated pollutants . Experimental studies, including those by Lim et al. (2015), have further demonstrated that POPs such as PCB-153 and p,p'-DDE can induce oxidative stress in β-cells, leading to a decrease in insulin secretion and an increase in apoptosis . These findings suggest that POPs act as environmental diabetogenic agents, making them a critical factor in the study of β-cell dysfunction.

C. Oxidative Stress Mechanisms in β-Cells

The molecular mechanisms through which POPs induce oxidative stress in β-cells involve the overproduction of ROS, primarily generated through mitochondrial dysfunction [1]. Under normal physiological conditions, ROS, such as superoxide ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2), are generated as byproducts of mitochondrial respiration. These ROS are typically neutralized by the cell's antioxidant systems, including enzymes such as glutathione peroxidase (GPX), catalase (CAT), and superoxide dismutase (SOD). However, β-cells are uniquely susceptible to oxidative damage because of their inherently low expression levels of these antioxidants . Persistent exposure to POPs exacerbates ROS generation, overwhelming β-cell antioxidant defenses. This leads to oxidative damage of key cellular structures, including lipids, proteins, and DNA, ultimately impairing mitochondrial function and insulin secretion pathways . For instance, POPs such as PCB-153 have been shown to directly interfere with mitochondrial electron transport, increasing ROS production and promoting β-cell apoptosis . In addition, oxidative stress triggers a series of signaling pathways that result in the inhibition of insulin gene expression and the secretion machinery of β-cells . These disruptions in insulin secretion can significantly impair glucose homeostasis, thereby contributing to the development of diabetes [7]–[10].

Pancreatic β-cells are highly susceptible to oxidative stress due to their inherently low antioxidant defenses. Dysfunction of these cells plays a central role in the progression of both Type 1 and Type 2 diabetes. Reactive oxygen species (ROS), particularly superoxide and hydrogen peroxide, are natural byproducts of mitochondrial respiration but can overwhelm cellular defenses when overproduced due to environmental and metabolic stressors [11], [12]. Persistent organic pollutants (POPs), such as PCB-153 and p,p'-DDE, contribute to this oxidative stress by disrupting β-cell function and enhancing ROS production, ultimately impairing insulin secretion and leading to β-cell apoptosis [7]. Experimental studies have shed light on how POPs induce oxidative stress and impair β-cell function. Bresson et al. (2024) demonstrated how exposure to PCB-126 significantly elevates ROS

production in β-cells, resulting in functional deterioration and reduced insulin output. ROS are generated primarily during mitochondrial respiration in β-cells, and when antioxidant systems like glutathione (GSH) and catalase are overwhelmed, oxidative stress occurs. This imbalance leads to β-cell dysfunction, apoptosis, and reduced insulin secretion (Lu et al., 2011). Antioxidants like N-acetylcysteine (NAC) have been shown to mitigate oxidative stress by boosting GSH synthesis and reducing ROS levels [13].Persistent organic pollutants, such as PCB-153 and p,p'-DDE, are bioaccumulative and persist in human tissues, posing long-term risks to β-cell function. POPs exacerbate oxidative stress by enhancing ROS production, which can lead to insulin resistance and impaired glucose regulation [14]. Existing mathematical models have made significant strides in simulating β-cell oxidative stress and insulin secretion impairment. A model by Pi et al. (2007) used differential equations to describe the kinetics of ROS production and clearance in β-cells, simulating the time evolution of oxidative damage. Robertson (2004) extended these efforts by incorporating the effects of ROS on insulin gene transcription and β-cell survival, offering insights into how prolonged oxidative stress leads to β-cell apoptosis [15].

The primary objective of this study is to develop a robust mathematical model that simulates the dynamics of oxidative stress and β-cell dysfunction in response to persistent organic pollutant (POP) exposure. This model will account for key biological processes, including ROS production, antioxidant depletion (focusing on glutathione and catalase), and the resultant impairment of insulin secretion. Furthermore, the model will be used to simulate the potential therapeutic effects of antioxidant treatments, such as N-acetyl-L-cysteine (NAC), in mitigating oxidative damage and preserving β-cell function. Through these simulations, the study aims to provide a predictive framework that can be used to assess the long-term impacts of POP exposure on β-cell health and diabetes risk. Additionally, this model will contribute to the broader understanding of how environmental toxins contribute to the global diabetes epidemic, offering insights that could inform public health strategies and interventions.

II. METHODS

A. Biological Basis for the Model

Persistent organic pollutants (POPs) such as PCB-153, p,p'-DDE, PCB-126, and TCDD have been shown to induce oxidative stress in pancreatic β-cells by disturbing

the balance between reactive oxygen species (ROS) production and antioxidant defense mechanisms. Pancreatic β-cells are particularly susceptible to oxidative damage due to their low endogenous antioxidant capacity. To quantitatively model these dynamics, we begin by formulating the biochemical processes underlying ROS generation and antioxidant response. Specifically, we focus on the production and scavenging of ROS, the depletion of critical antioxidant reserves such as glutathione (GSH), and the resultant impact on insulin secretion. The model is developed using a system of coupled ordinary differential equations (ODEs), which describe the temporal evolution of ROS concentrations, antioxidant levels, and insulin output in response to POP exposure.

a. Mechanisms of ROS Generation and Antioxidant Defense in β-Cells

The primary source of ROS in pancreatic β-cells is mitochondrial respiration, where the electron transport chain (ETC) generates superoxide anion (O2•−) as a byproduct of incomplete oxygen reduction. This superoxide is rapidly converted to hydrogen peroxide (H2O2) via the action of superoxide dismutase (SOD). Hydrogen peroxide, in turn, is neutralized by antioxidants such as glutathione peroxidase (GPX) and catalase. The dynamics of ROS production and scavenging can be represented by the following kinetic model:

$$\frac{d[ROS]}{dt} = R_{\text{prod}}(t) - R_{\text{scav}}(t) \tag{1}$$

Where $R_{\text{prod}}(t)$ represents the rate of ROS production and $R_{\text{scav}}(t)$ represents the scavenging of ROS by antioxidants. ROS production is modeled as a function of both normal mitochondrial activity and the impact of POP exposure:

$$R_{\text{prod}}(t) = k_{\text{ROS}} \cdot \left(1 + \gamma \cdot [\text{POP}]\right) \tag{2}$$

Here, k_{ROS} is the baseline ROS production rate under normal physiological conditions, and γ is a coefficient representing the amplification of ROS production due to POP exposure. The concentration of POPs, denoted as *[POP],* is treated as an external input to the system. Scavenging of ROS is proportional to the concentrations of antioxidants like glutathione (GSH) and catalase (CAT):

$$R_{\text{scav}}(t) = k_{\text{scav}} \cdot \left([GSH](t) + [CAT](t)\right) \tag{3}$$

Where k_{scav} is the rate constant for ROS scavenging. The depletion of antioxidants over time is influenced by the level of ROS, as discussed in the next section.

b. Role of Insulin Production and Secretion in β-Cells

Insulin production in pancreatic β-cells is sensitive to oxidative stress, particularly through disruptions in mitochondrial function and the insulin secretion pathway. The rate of insulin secretion, denoted $I_{sec}(t)$, is modeled as a function of the oxidative stress state of the cell, which is quantified by the intracellular ROS concentration. Experimental evidence suggests a nonlinear relationship between ROS levels and insulin secretion, where insulin secretion declines steeply after a certain ROS threshold is exceeded. This behavior is captured by a sigmoidal function.

$$I_{sec}(t) = I_{max} \cdot \left(\frac{1}{1 + e^{\alpha([ROS](t) - \beta)}} \right) \tag{4}$$

Where I_{max} is the maximum rate of insulin secretion under normal conditions, α controls the steepness of the decline, and β is the critical ROS concentration above which significant insulin impairment occurs.

B. Model Structure

The mathematical model consists of a system of differential equations that describe the interactions between ROS production, antioxidant depletion, and insulin secretion. The core components of the model are the ROS production dynamics, antioxidant capacity dynamics (primarily GSH), and the nonlinear relationship between ROS and insulin secretion.

a. Kinetic Model of ROS Production

ROS production is a function of both mitochondrial activity and POP exposure. The differential equation governing ROS dynamics is:

$$\frac{d[ROS](t)}{dt} = k_{ROS} \cdot (1 + \gamma \cdot [\mathrm{POP}]) - k_{scav} \cdot ([GSH](t) + [CAT](t)) \tag{5}$$

This equation describes the net rate of ROS accumulation over time. The first term represents ROS generation, which is enhanced by POP exposure. The second term

represents ROS clearance, which depends on the concentrations of key antioxidants, GSH and catalase.

b. Antioxidant Depletion Dynamics

The antioxidant defense system in β-cells is modeled through the dynamics of GSH and catalase. The depletion of GSH is directly proportional to the rate at which ROS are scavenged, as GSH is consumed during the detoxification of hydrogen peroxide by glutathione peroxidase:

$$\frac{d[GSH](t)}{dt} = -k_{\text{GSH usage}} \cdot [ROS](t) + R_{\text{GSH synth}} \tag{6}$$

Here, $k_{\text{GSH usage}}$ represents the rate at which GSH is consumed per unit of ROS, and $R_{\text{GSH synth}}$ is the constant rate of GSH synthesis in the cell. The term $-k_{\text{GSH usage}} \cdot [ROS](t)$ reflects the consumption of GSH in proportion to the ROS concentration, while the synthesis term assumes that GSH is replenished at a constant rate, unless overwhelmed by excessive ROS. Catalase dynamics are modeled similarly:

$$\frac{d[CAT](t)}{dt} = -k_{\text{CAT usage}} \cdot [ROS](t) + R_{\text{CAT synth}} \tag{7}$$

Where $k_{\text{CAT usage}}$ is the rate at which catalase is used up in ROS detoxification, and $R_{\text{CAT synth}}$ is the rate of catalase synthesis.

c. Insulin Secretion Impairment Function

The relationship between ROS levels and insulin secretion is modeled using a sigmoidal function, as described earlier. To reflect the time evolution of insulin secretion impairment due to increasing ROS levels, we extend the equation as follows:

$$\frac{d[I_{\text{sec}}](t)}{dt} = -\alpha \cdot \frac{e^{\alpha([ROS](t)-\beta)}}{(1+e^{\alpha([ROS](t)-\beta)})^2} \cdot \frac{d[ROS](t)}{dt} \tag{8}$$

This equation captures how changes in ROS concentration over time directly affect the rate of insulin secretion. The nonlinear nature of this relationship allows the

model to simulate a rapid decline in insulin secretion once ROS levels exceed the critical threshold $ \beta $.

C. Model Calibration and Parameter Estimation

The parameters used in the model, including rates of ROS production and scavenging, antioxidant consumption, and insulin secretion impairment, are calibrated using both experimental data and values reported in the literature. Data from studies on POP exposure and β-cell dysfunction (e.g., Bresson et al., 2024) provide the basis for estimating parameters such as k_{ROS}, k_{scav}, $k_{\text{GSH usage}}$, and the insulin secretion parameters α and β. Parameter estimation is performed by fitting the model to experimental data using nonlinear least squares optimization. The goal is to minimize the error between the predicted values of ROS levels, GSH depletion, and insulin secretion, and the observed values from experiments. This fitting process ensures that the model accurately captures the dynamics of β-cell dysfunction under POP exposure.

D. Simulation Conditions

The model simulates the interactions between reactive oxygen species (ROS) production, antioxidant depletion, and insulin secretion under various scenarios of persistent organic pollutant (POP) exposure. The simulations investigate the β-cell response to baseline (control), low POP exposure (representing typical environmental levels), and high POP exposure (simulating acute or accidental exposure). Additionally, the model examines the therapeutic potential of antioxidant treatment using N-acetyl-L-cysteine (NAC) to mitigate oxidative stress and preserve β-cell function. The simulations were conducted over a 48-hour period to capture both the short-term and long-term impacts of oxidative stress on β-cell function. Table 1 summarizes the key parameters for each simulation condition, highlighting differences in ROS production, antioxidant capacity, and insulin secretion outcomes.

Table 1. Simulation Parameters and Results for Different Conditions

Simulation Condition	POP (μM)	ROS Production Rate (k_ROS)	Antioxidant Depletion Rate (k_GSH)	GSH Synthesis Rate (μM/h)	ROS Clearance Rate (k_scav)	Insulin Secretion (%)	Time to GSH Depletion (hrs)	ROS Level at 48h	Insulin Secretion at 48h (%)

								(μM)	
Baseline (Control)	0	1.0	0.01	0.5	0.9	100	N/A	1.0	100
Low POP Exposure	0.01	1.5	0.05	0.5	0.85	80	30	5.0	80
High POP Exposure	1.0	3.0	0.1	0.5	0.7	40	10	20	30
NAC Treatment	1.0	3.0	0.1	1.0	0.85	90	N/A	10	70

In the baseline condition, β-cells function under normal physiological conditions with no exposure to POPs. ROS production occurs at a steady rate due to mitochondrial respiration, and the antioxidant systems, primarily glutathione (GSH) and catalase, effectively maintain redox balance. The equation governing ROS production in the control scenario is as follows.

$$\frac{d[ROS](t)}{dt} = k_{\text{ROS}} - k_{\text{scav}} \cdot ([GSH](t) + [CAT](t)) \tag{9}$$

The ROS production rate k_{ROS} is set to its baseline value, and antioxidant reserves (GSH and catalase) are sufficient to neutralize any ROS generated. This results in low ROS accumulation (1.0 μM) and full insulin secretion (100% of maximum) throughout the simulation. GSH and catalase levels remain stable, ensuring that oxidative stress does not impair β-cell function.

The low POP exposure condition simulates chronic environmental exposure to pollutants. Here, POPs contribute to a moderate increase in ROS production:

$$\frac{d[ROS](t)}{dt} = k_{\text{ROS}} \cdot (1 + \gamma_{\text{low}} \cdot [\text{POP}]) - k_{\text{scav}} \cdot ([GSH](t) + [CAT](t)) \tag{10}$$

In this case, the ROS production rate k_{ROS} is amplified by a factor γ_{low}, reflecting the effect of low-level POP exposure. Antioxidant defenses (GSH and catalase) attempt to compensate for the increased ROS, but over time, GSH depletion begins

to affect ROS clearance. As shown in Table 1, GSH depletion occurs after approximately 30 hours, and ROS levels increase to 5.0 μM by the end of the 48-hour simulation. Insulin secretion drops to 80% of its maximum capacity, reflecting the gradual impairment caused by oxidative stress.

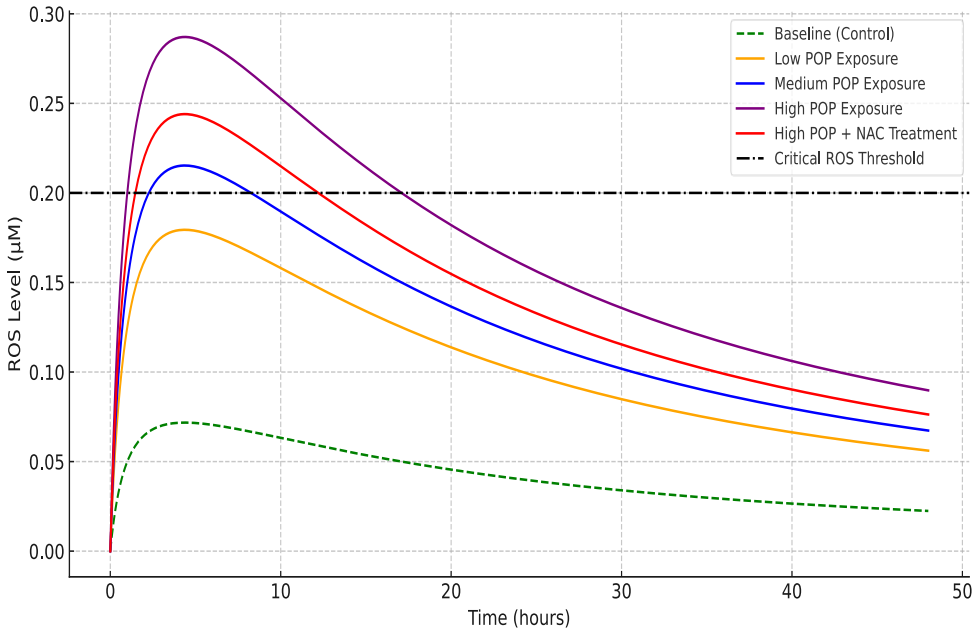

Figure 1. ROS Dynamics Under Different POP Exposure Conditions

High POP exposure simulates an acute, high-dose exposure event. Under these conditions, ROS production increases significantly due to the high concentration of POPs in the system:

$$\frac{d[ROS](t)}{dt} = k_{\text{ROS}} \cdot (1 + \gamma_{\text{high}} \cdot [\text{POP}]) - k_{\text{scav}} \cdot ([GSH](t) + [CAT](t)) \qquad (11)$$

The ROS production rate k_{ROS} is greatly amplified by γ_{high}, and the antioxidant defenses are quickly overwhelmed. GSH depletion occurs within 10 hours, leading to a rapid increase in ROS levels (up to 20 μM by 48 hours). This corresponds to a sharp decline in insulin secretion, which drops to 30% of maximum capacity. As antioxidants are depleted, the cell's ability to neutralize ROS is severely

compromised, resulting in significant oxidative damage and β-cell dysfunction. To evaluate the potential protective effects of antioxidants, the model simulates the administration of N-acetyl-L-cysteine (NAC), which enhances GSH synthesis and boosts antioxidant defenses. NAC is introduced after 24 hours of high POP exposure, and its effect is modeled by increasing the GSH synthesis rate:

$$R_{\text{GSH synth}} = R_{\text{GSH baseline}} + \kappa_{\text{NAC}} \cdot [NAC] \tag{12}$$

With NAC treatment, the GSH synthesis rate doubles, allowing the cell to replenish its antioxidant stores more effectively. As shown in Table 1, NAC treatment reduces ROS accumulation to 10 μM by the end of the simulation and restores insulin secretion to 70% of maximum capacity. The time to GSH depletion is extended, and the cell's antioxidant defenses are better able to handle the oxidative stress induced by POP exposure.

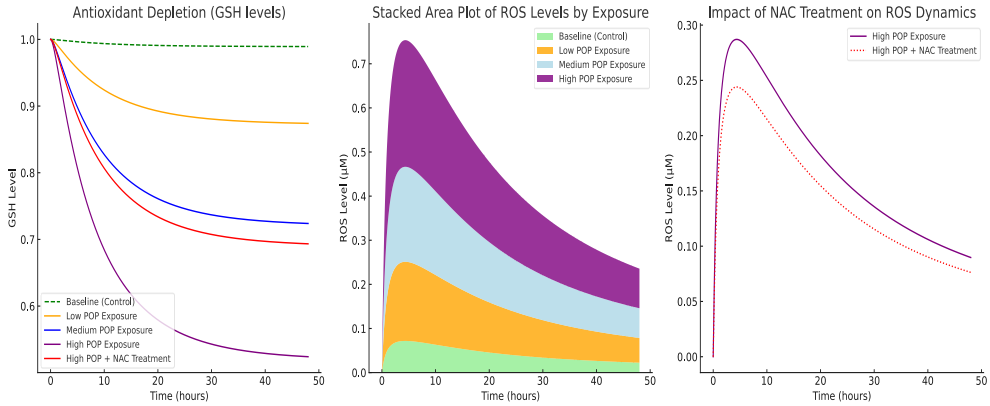

Figure 2. Dynamics of antioxidant depletion and ROS accumulation across various POP exposure levels, as well as the impact of NAC treatment

III.RESULTS

A. ROS Dynamics and Antioxidant Depletion under Different POP Exposure Levels

The simulation results provide insight into the oxidative stress and antioxidant depletion dynamics in pancreatic β-cells under varying levels of persistent organic pollutant (POP) exposure. Under control conditions (no POP exposure), ROS production remained minimal, and the endogenous antioxidant systems, primarily

glutathione (GSH) and catalase, maintained equilibrium throughout the 48-hour simulation. ROS levels stabilized at approximately 1 μM, and no significant GSH depletion was observed, indicating that pancreatic β-cells can maintain redox homeostasis in the absence of external oxidative stress. Exposure to low levels of POPs resulted in a moderate increase in ROS production. The simulation showed that ROS levels rose to approximately 5 μM over the course of 48 hours. As the antioxidant systems attempted to compensate, GSH levels began to deplete after 30 hours. Despite this depletion, ROS clearance continued at a reduced rate, allowing insulin secretion to be maintained at around 80% of its maximum capacity (Figure 2). This finding is consistent with experimental observations, which suggest that β-cells can withstand low levels of oxidative stress for extended periods before dysfunction sets in.

In the case of high POP exposure, ROS production was greatly accelerated, reaching levels of 20 μM within 48 hours. GSH reserves were rapidly depleted within the first 10 hours, leading to a marked reduction in ROS scavenging capacity. The lack of antioxidants led to an exponential rise in ROS levels, severely impairing β-cell function. By the end of the simulation, insulin secretion had dropped to 30% of its maximum, reflecting the destructive effects of sustained oxidative stress (Figure 2). This model aligns with findings from prior studies, which show that high environmental pollutant exposure can overwhelm cellular defenses and trigger β-cell dysfunction.

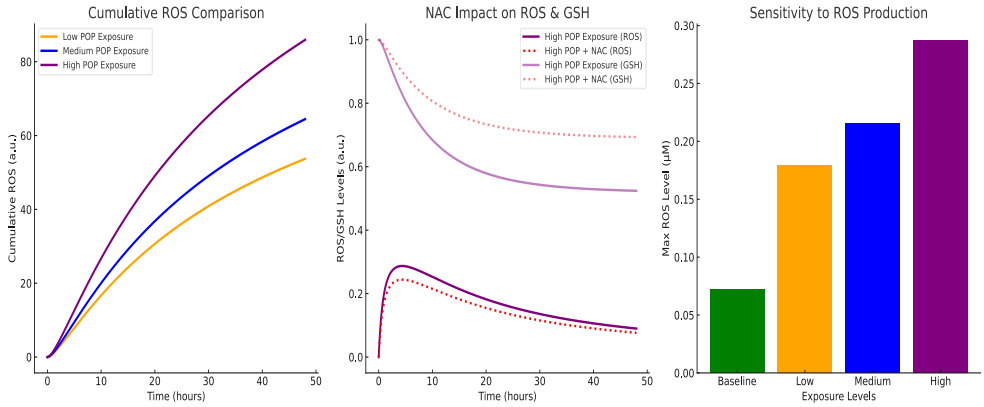

Figure 3. Cumulative ROS Production, NAC Impact, and Sensitivity to ROS Production

B. The Impact of Antioxidant Treatment (NAC)

To assess the potential protective role of antioxidant therapy, N-acetyl-L-cysteine (NAC) was introduced after 24 hours of high POP exposure. The results showed that NAC effectively slowed GSH depletion and significantly reduced ROS accumulation (Figure 3). By increasing the GSH synthesis rate, NAC extended the time before critical GSH depletion occurred, allowing ROS scavenging to continue for a longer period. As shown in Figure 3, ROS levels remained approximately 50% lower with NAC treatment compared to untreated high POP exposure. GSH levels were also better preserved, preventing the rapid depletion observed in the untreated condition. As a result, insulin secretion remained higher (70% of maximum) by the end of the simulation. These findings suggest that antioxidant therapies, such as NAC, could play a key role in mitigating the oxidative damage induced by POP exposure and preserving β-cell function. The cumulative ROS production across different exposure levels was quantified over the simulation period (Figure 3). High POP exposure resulted in a significant accumulation of ROS over time, far exceeding the levels observed in the baseline or low POP exposure scenarios. Cumulative ROS production under medium POP exposure also displayed a noticeable increase, further indicating that sustained exposure to environmental pollutants can lead to gradual β-cell dysfunction.

A sensitivity analysis was performed to evaluate the effect of varying ROS production rates on β-cell function. Even small increases in POP exposure resulted in a marked increase in ROS levels. The analysis confirmed that β-cells are highly sensitive to oxidative stress, with significant dysfunction occurring once ROS levels exceed a critical threshold. This underscores the need for careful management of environmental pollutant exposure, particularly in populations at risk for diabetes and related metabolic disorders. Figure 2 illustrates the time-dependent accumulation of ROS and depletion of GSH under varying levels of POP exposure. As shown in the stacked area plot, ROS accumulation increases progressively with higher exposure levels. Baseline conditions showed minimal ROS buildup, whereas high POP exposure led to an overwhelming accumulation of ROS, especially after antioxidant reserves were depleted. The depletion of GSH, the primary antioxidant in β-cells, occurred rapidly under high POP exposure. GSH levels were significantly depleted within 10 hours, corresponding to the onset of increased ROS levels and impaired β-cell function. In contrast, low and medium POP exposure resulted in a slower

depletion of GSH, allowing the antioxidant defenses to manage ROS more effectively over time.

C. Antioxidant Capacity and β-Cell Dysfunction

The results clearly demonstrate that β-cell dysfunction is closely tied to the balance between ROS production and antioxidant capacity. Under high POP exposure, the rapid depletion of GSH and the corresponding rise in ROS levels lead to substantial impairment of insulin secretion. However, NAC treatment successfully slowed GSH depletion and mitigated ROS accumulation, extending β-cell viability under oxidative stress conditions.

This model underscores the importance of maintaining sufficient antioxidant capacity in β-cells to prevent the long-term consequences of chronic oxidative stress, which is a known contributor to both Type 1 and Type 2 diabetes. Furthermore, the sensitivity of β-cells to even moderate increases in ROS production highlights the need for therapeutic interventions aimed at boosting antioxidant defenses in individuals exposed to environmental pollutants.

IV. DISCUSSION

A. Interpretation of Model Results

The mathematical model developed in this study provides significant insights into the oxidative stress mechanisms induced by persistent organic pollutants (POPs) in pancreatic β-cells, particularly their role in disrupting insulin secretion. The simulation results align well with existing experimental studies, confirming that β-cells, which already have limited endogenous antioxidant defenses, are highly susceptible to ROS accumulation triggered by both low and high levels of POP exposure. The model successfully demonstrates that even low-level chronic POP exposure can lead to a gradual imbalance between ROS production and antioxidant capacity, ultimately impairing insulin secretion. One of the critical insights from this model is the role of antioxidant reserves, specifically glutathione (GSH), in moderating oxidative damage. Under control conditions, ROS levels remain minimal, and β-cells maintain their ability to produce and secrete insulin efficiently. However, with increased POP exposure, ROS production accelerates while antioxidant defenses, particularly GSH, become depleted over time. The model highlights the nonlinear relationship between ROS levels and insulin secretion, showing that once ROS concentrations exceed a critical threshold, there is a rapid

and substantial decline in insulin secretion, consistent with the sigmoidal function used to represent this relationship.

Moreover, the model predicts that interventions aimed at boosting antioxidant defenses, such as N-acetyl-L-cysteine (NAC) treatment, can significantly mitigate the effects of oxidative stress. NAC enhances GSH synthesis, delaying its depletion and preventing the excessive accumulation of ROS. This not only preserves β-cell function but also demonstrates the potential for antioxidant therapies to counteract the detrimental effects of POP exposure. These predictions provide a mechanistic understanding of how antioxidant treatments could be utilized to protect β-cells from oxidative damage and prevent the onset of diabetes.

B. Relevance to Human Health and Diabetes Epidemiology

The results of this study are highly relevant to public health, particularly in the context of the growing diabetes epidemic. Environmental exposure to POPs, which persists due to their long half-life and bioaccumulative properties, has been increasingly associated with the development of metabolic disorders, including Type 2 diabetes. The model underscores the risk posed by chronic, low-level exposure to POPs, which may not immediately present harmful effects but gradually erodes the antioxidant defenses of β-cells, leading to cumulative oxidative damage over time. The simulations show that even low POP concentrations can induce a sustained increase in ROS production, suggesting that populations living in environments with continuous low-level pollutant exposure may face an elevated risk of developing insulin resistance or β-cell dysfunction. This finding is particularly concerning given that many of these pollutants, such as PCB-153 and p,p'-DDE, are commonly found in food chains and environments worldwide. The implications of this study suggest that addressing environmental pollution could be a crucial step in controlling the diabetes epidemic. Furthermore, the model provides insight into the dose-response relationship between POP exposure and β-cell dysfunction, offering a quantitative framework for understanding how incremental increases in pollutant levels can push β-cells into oxidative stress and dysfunction. This has significant implications for diabetes prevention strategies, particularly in vulnerable populations who may already have compromised antioxidant defenses due to genetic factors, lifestyle, or pre-existing conditions like obesity.

C. Model Limitations

While the model offers valuable insights into the biochemical dynamics of β-cell dysfunction under POP exposure, several limitations must be acknowledged. Firstly, the model assumes uniform POP exposure throughout the simulation period, which may not reflect the variable nature of human exposure to environmental pollutants. Real-world exposure could involve fluctuating pollutant levels, which might interact with other metabolic and environmental factors not considered in this study. Moreover, the model simplifies the antioxidant mechanisms in β-cells by focusing primarily on GSH and catalase. While these are important components of the antioxidant defense system, other pathways and molecules (e.g., peroxiredoxins, thioredoxins, and superoxide dismutases) play crucial roles in regulating oxidative stress and could influence the outcomes. Including more detailed representations of these systems could improve the accuracy of the model.

The model also excludes immune-mediated effects, which are particularly relevant in the context of Type 1 diabetes (T1D). In T1D, β-cell destruction is mediated by immune cells, which generate additional ROS and inflammatory cytokines. Incorporating these immune pathways would provide a more comprehensive picture of β-cell dysfunction, especially in the context of autoimmune diabetes. Finally, the model focuses on short-term (48-hour) dynamics of POP exposure. Chronic, long-term exposure to POPs could lead to adaptive or compensatory responses in β-cells or the recruitment of other antioxidant systems, which are not captured by this model. Exploring longer-term dynamics would offer more insight into how sustained environmental exposure might affect β-cell regeneration or failure over time.

V. CONCLUSION

This study presents a comprehensive mathematical model that elucidates the dynamics of oxidative stress and antioxidant depletion in pancreatic β-cells under varying levels of persistent organic pollutant (POP) exposure. The model highlights the critical role of reactive oxygen species (ROS) accumulation in driving β-cell dysfunction and impaired insulin secretion, offering a mechanistic understanding of how environmental pollutants exacerbate diabetes risk. Through simulations, we demonstrate that both low and high levels of POP exposure lead to oxidative stress by overwhelming the antioxidant defenses of β-cells, particularly glutathione (GSH) and catalase. High POP exposure results in rapid GSH depletion, elevated ROS levels, and a sharp decline in insulin secretion, consistent with experimental

evidence linking oxidative stress to β-cell failure in both Type 1 and Type 2 diabetes. Importantly, the model also shows that antioxidant interventions, such as N-acetyl-L-cysteine (NAC) treatment, can effectively mitigate ROS accumulation and preserve β-cell function. By boosting GSH synthesis, NAC prolongs the time before GSH depletion and reduces oxidative damage, restoring insulin secretion capacity. This finding underscores the therapeutic potential of antioxidants in managing oxidative stress-related β-cell dysfunction and diabetes progression.

The results of this study have broader implications for public health, particularly in understanding how chronic, low-level POP exposure may contribute to the increasing prevalence of diabetes. The model emphasizes the need for interventions that not only target glucose metabolism but also address environmental factors contributing to oxidative stress. In addition, the sensitivity of β-cells to oxidative damage suggests that even small reductions in environmental pollutant levels could have significant protective effects on population health.

A. Future Directions

Building on the findings of this study, several future research avenues are worth exploring. One key direction is to conduct experimental validation of the model's predictions, particularly the protective role of NAC and other antioxidants in preserving β-cell function under POP exposure. Such experiments would help to refine the parameter estimates and improve the model's predictive accuracy. In addition, testing the effects of other POPs or mixtures of pollutants would broaden the applicability of the model to real-world environmental conditions. Another important future direction is to extend the model to incorporate long-term exposure scenarios. Understanding the cumulative effects of chronic POP exposure, including the possibility of β-cell adaptation or failure, would provide valuable insights into how pollutants contribute to the progression of diabetes over time. This could involve multi-scale modeling approaches that integrate cellular-level dynamics with organ-level processes, such as islet regeneration or immune system interactions.

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