

Communication

A Quantum-Biochemical Model of AA-5-HT-Induced Cytotoxicity in HL-60 Cells via FAAH Inhibition and Cannabinoid Receptor–Mediated Signal Interference

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Abstract

Acute promyelocytic leukemia (APL) remains one of the most aggressive hematological malignancies, necessitating the discovery of novel therapeutic agents with improved efficacy and reduced toxicity. N-arachidonoyl-5-hydroxytryptamine (AA-5-HT), a hybrid indole–fatty acid amide compound isolated from *Dialium corbisieri*, has demonstrated potent cytotoxic activity in HL-60 leukemia cells, characterized by G₁ phase cell cycle arrest at low micromolar concentrations (2.3 μM). Despite these promising findings, its mechanism of action remains incompletely understood. Here, we propose a quantum-biochemical hypothesis integrating molecular pharmacology with principles derived from quantum theory to explain AA-5-HT-induced cytotoxicity. We hypothesize that AA-5-HT inhibits fatty acid amide hydrolase (FAAH), leading to accumulation of anandamide (AEA), which in turn activates Gi/o-coupled cannabinoid receptors (CB₁/CB₂). This activation suppresses the PI3K/AKT signaling pathway, resulting in decreased AKT phosphorylation, upregulation of cyclin-dependent kinase inhibitors (p21, p27), reduced retinoblastoma protein phosphorylation, and consequent G₁ arrest. From a quantum-biochemical perspective, AA-5-HT acts as a perturbator that shifts intracellular signaling probabilities, promoting destructive interference of pro-survival pathways and stabilizing a non-proliferative cellular state. This framework provides a novel conceptual model for understanding anticancer mechanisms and suggests new experimental directions for validating AA-5-HT as a therapeutic candidate.

Keywords

Acute Promyelocytic Leukemia (APL), N-arachidonoyl-5-hydroxytryptamine (AA-5-HT), FAAH Inhibition, Cytotoxicity, Quantum Biochemical

1. Introduction

Acute promyelocytic leukemia (APL) represents a highly aggressive subtype of acute myeloid leukemia characterized by rapid disease progression and high early mortality [7]. Despite advances in targeted therapies, including differentiation-based treatments, therapeutic resistance and adverse effects

remain critical limitations [29].

Natural products constitute an important source of bioactive compounds with diverse pharmacological properties. Their structural complexity and multi-target potential make them

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particularly valuable in cancer therapy [2]. Among these, compounds derived from *Dialium corbisieri* have recently attracted attention due to their biological activity [10].

N-arachidonoyl-5-hydroxytryptamine (AA-5-HT), a member of the N-fatty acyl-5-hydroxytryptamine family, possesses a hybrid structure combining an indole moiety and a fatty acid chain. This dual structure enables interaction with both neurotransmitter-related and lipid signaling pathways [25]. Previous studies have demonstrated its analgesic activity through antagonism of TRPV1 receptors, while recent findings indicate potent cytotoxic effects in HL-60 leukemia cells, including induction of G₁ phase arrest at low micromolar concentration [10].

However, the molecular basis of this cytotoxic activity remains poorly understood. The present work proposes a mechanistic hypothesis integrating classical biochemical pathways with a quantum-inspired framework to better explain the observed effects.

2. Biological Background

Cancer cells exhibit profound metabolic reprogramming,

particularly in lipid metabolism. Fatty acids contribute to Energy production, Membrane biosynthesis, Signal transduction [4, 26].

Alterations in lipid metabolism support tumor growth and survival, making lipid-related pathways attractive therapeutic targets [17, 23].

Indole alkaloids are also known to exert diverse anticancer effects, including apoptosis, autophagy, ferroptosis, and cell cycle arrest [5, 13]. The hybrid nature of AA-5-HT suggests that it may disrupt both lipid-mediated and signaling pathways in cancer cells.

3. Hypothesis

We hypothesize that:

AA-5-HT induces cytotoxicity in HL-60 cells through FAAH inhibition, leading to anandamide accumulation, activation of CB₁/CB₂ receptors, suppression of PI3K/AKT signaling, and induction of G₁ cell cycle arrest [1, 6, 12, 27].

Furthermore, we propose that this process can be interpreted within a quantum-biological framework, where intracellular signaling operates as a probabilistic system influenced by molecular perturbations.

4. Proposed Mechanism of Action

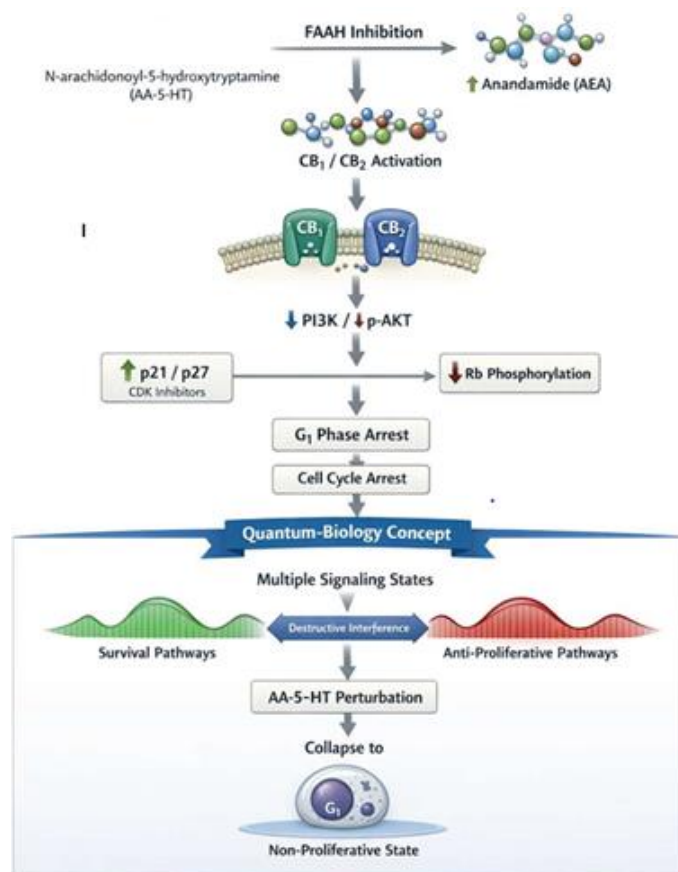


Figure 1. A proposed mechanism of AA-5-HT induced cytotoxicity in HL-60 cells and Non-proliferative state.

4.1. FAAH Inhibition and Endocannabinoid Accumulation

AA-5-HT inhibits FAAH, the enzyme responsible for the degradation of anandamide (AEA). This results in increased intracellular AEA levels and enhanced activation of cannabinoid receptors [6, 25].

4.2. Cannabinoid Receptor Activation

Accumulated AEA activates CB₁ and CB₂ receptors, which are coupled to inhibitory Gi/o proteins. This activation suppresses downstream signaling pathways involved in cell survival [15, 24].

4.3. Suppression of PI3K/AKT Signaling

CB receptor activation leads to inhibition of the PI3K/AKT pathway, a critical regulator of cancer cell survival and proliferation. This results in decreased AKT phosphorylation and reduced pro-survival signaling [11, 31].

4.4. Induction of G₁ Cell Cycle Arrest

The inhibition of AKT signaling promotes [18, 28]:

- 1) Upregulation of CDK inhibitors (p21, p27)
- 2) Decreased phosphorylation of retinoblastoma protein (Rb)
- 3) Arrest of the cell cycle in the G₁ phase

4.5. Independence from Ca²⁺ Signaling

The absence of calcium modulation suggests that AA-5-HT does not act through TRPV1-mediated calcium influx, supporting a Gi/kinase-dependent mechanism.

5. Methods and Theoretical Modeling

5.1. Modeling Framework

To describe the cytotoxic effects of N-arachidonoyl-5-hydroxytryptamine (AA-5-HT) in HL-60 cells, we developed a quantum-inspired probabilistic model of intracellular signaling. The model treats cellular fate as a dynamic system governed by competing signaling networks, represented as a superposition of functional states [14, 16].

The cellular state vector is defined as:

$$|\Psi(t)\rangle = \alpha(t)|S\rangle + \beta(t)|A\rangle$$

where $|S\rangle$ denotes the proliferative (survival) state and $|A\rangle$ denotes the anti-proliferative (G₁ arrest) state. The coefficients $\alpha(t)$ and $\beta(t)$ represent time-dependent probability amplitudes, subject to the normalization condition:

$$|\alpha(t)|^2 + |\beta(t)|^2 = 1$$

This formulation allows the system to dynamically evolve between competing biological outcomes.

5.2. Effective Signaling Hamiltonian

The intracellular signaling network is represented by an effective Hamiltonian operator:

$$H = H_{AKT} + H_{CB} + H_{AA-5-HT}$$

where:

H_{AKT} : represents the pro-survival PI3K/AKT signaling pathway

H_{CB} : represents cannabinoid receptor-mediated signaling

$H_{AA-5-HT}$: represents the perturbative effect of AA-5-HT

AA-5-HT is modeled as a perturbation acting on enzymatic and receptor components:

$$H_{AA-5-HT} = -\lambda_1 \wedge FFAAH + \lambda_2 \wedge RCB$$

Where $\wedge FFAAH$ denotes FAAH enzymatic activity, $\wedge RCB$ denotes CB₁/CB₂ receptor activation [19, 21], and λ_1, λ_2 are coupling constants describing interaction strengths.

5.3. Anandamide Kinetics

The intracellular concentration of anandamide (AEA) is modeled using a first-order kinetic equation:

$$\left(\frac{d[AEA]}{dt}\right) = k_s - k_d^{FAAH}[AEA]$$

Where k_s is the synthesis rate and k_d^{FAAH} is the degradation rate mediated by FAAH.

In the presence of AA-5-HT, FAAH activity is inhibited such that:

$$k_d^{FAAH} \rightarrow k_d^{FAAH}(1 - \eta)$$

where η represents the inhibition efficiency ($0 \leq \eta \leq 1$). This leads to accumulation of AEA and enhanced receptor activation [22]:

5.4. Transition Probability and State Evolution

The probability of transition from the survival state to the arrested state is given by:

$$\frac{(d[p_{AKT}])}{dt} = k_{PI3K} - k_{inh} \cdot f([CB])$$

Where:

k_{PI3K} : represents basal activation

k_{inh} : represents inhibition strength

$f([CB])$: is a function proportional to CB receptor activation, itself dependent on AEA concentration

Assuming proportionality:

$$f([CB]) \propto [AEA]$$

the steady-state AKT activity can be approximated as:

$$[pAKT] \propto (1 + \gamma[AEA])^{-1}$$

where γ is a scaling constant describing sensitivity to AEA.

5.5. Transition Probability and State Evolution

The probability of transition from the survival state to the arrested state is given by:

$$P_{S \rightarrow A} = |\langle A | H_{AA-5-HT} | S \rangle|^2$$

This transition probability increases with: FAAH inhibition, CB receptor activation and Suppression of AKT signaling.

The temporal evolution of the system follows a Schrödinger-like equation [3, 20].

$$i\hbar \left(\frac{d}{dt} \right) |\Psi(t)\rangle = H |\Psi(t)\rangle$$

where H is the effective Hamiltonian defined above.

5.6. Interference of Signaling Pathways

To account for the interaction between competing pathways, the total survival amplitude is expressed as:

$$A_S = A_{AKT} + A_{CB}$$

Where:

A_{AKT} is the pro-survival amplitude

A_{CB} is the inhibitory amplitude

The survival probability is:

$$P_S = |A_S|^2$$

Destructive interference occurs when:

$$A_{CB} \approx -A_{AKT}$$

leading to suppression of survival signaling.

5.7. Cell Cycle Regulation Operator

Cell cycle progression is represented by an effective operator:

$$\hat{C} = \hat{C}_{CDK} - \hat{I}_{\frac{p21}{p27}}$$

Where $\hat{C}_{CDK}$ promotes progression and $\hat{I}_{\frac{p21}{p27}}$ represents inhibition by cyclin-dependent kinase inhibitors.

AA-5-HT shifts the expectation value:

$$\langle \hat{C} \rangle \rightarrow 0$$

corresponding to arrest at the G₁ phase.

5.8. Outcome Probability and State Collapse

The probability of the anti-proliferative outcome is:

$$(A) = |\beta(t)|^2$$

When:

$$|\beta(t)|^2 \rightarrow 1$$

the system converges to the arrested state:

$$|\Psi\rangle \rightarrow |A\rangle$$

representing G₁ cell cycle arrest and loss of proliferative capacity.

6. Significance

This study provides:

- 1) A novel mechanistic insight into AA-5-HT activity [13];
- 2) A quantum-inspired framework for understanding complex signaling systems [9, 16, 20];
- 3) A potential strategy for targeting lipid signaling in cancer therapy [26], cannabinoid anticancer mechanism [13, 30]; and Endocannabinoid pharmacology [8, 23].

The integration of quantum concepts into biological systems may open new avenues for drug discovery and mechanistic interpretation.

7. Conclusion

AA-5-HT represents a promising anticancer candidate capable of inducing G₁ cell cycle arrest in HL-60 cells through modulation of endocannabinoid signaling and inhibition of the PI3K/AKT pathway.

The proposed quantum-biological model offers a new perspective on intracellular signaling, suggesting that therapeutic agents can influence cellular outcomes by altering probabilistic signaling dynamics. This framework warrants further experimental validation and may contribute to the development of innovative anticancer strategies.

Abbreviations

AA-5-HT	N-arachidonoyl-5-hydroxytryptamine
AEA	Endocannabinoid ligand anandamide
AKT	Protein Kinase B (Akt straintransforming)

APL	Acute Promyelocytic Leukemia
CB1/CB2	As receptors are two primary cellular targets of the endocannabinoid system, which regulates critical bodily functions like mood, pain, appetite and immune response
FAAH	Fatty Acid Amid Hydrolase
HL-60	Acute Promyelocytic Leukemia Cell
PI3K	phosphatidylinositol-3kinase
P21	a cyclin-dependent kinase (CDK) inhibitor primarily regulates the cell cycle by enforcing G1 and G2/M phase arrests in response to DNA damage.
P27	is a critical regulatory that halts cell division by binding to and inhibiting cyclin-dependent kinases (CDKs). As a master gatekeeper of cell growth, its primary function is to prevent cells from the G1 phase to the (S) Phase, effectively stopping uncontrolled proliferation.
TRPV1	Transient Receptor Potential Vanilloid 1

Author Contributions

Atakuru Dradre Paulin: Conceptualization, Data curation, Formal Analysis, Methodology

Conflicts of Interest

The author declares no conflicts of interest.

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