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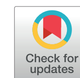
A swinging seesaw as a novel model mechanism for time-dependent hormesis under dose-dependent stimulatory and inhibitory effects: A case study on the toxicity of antibacterial chemicals to *Aliivibrio fischeri*



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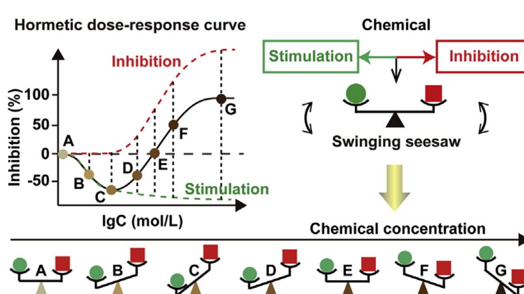
HIGHLIGHTS

- The chemicals induce stimulatory and inhibitory effects on the bioluminescence.
- The dose-dependent opposing effects of chemical make up a swinging seesaw.
- Different swings of the seesaw result in time-dependent hormetic phenomenon.
- The biological seesaw model provides a dose-time-dependent mechanism for hormesis.

GRAPHICAL ABSTRACT



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ABSTRACT

Hormesis occurs frequently in broadly ranging biological areas (e.g. plant biology, microbiology, biogerontology), toxicology, pharmacology and medicine. While numerous mechanisms (e.g. receptor and pathway mediated pathway responses) account for stimulatory and inhibitory features of hormetic dose responses, the vast majority emphasizes the inclusion of many doses but only one timepoint or use of a single optimized dose that is assessed over a broad range of timepoints. In this paper, a toxicity study was designed using a large number of properly spaced doses with responses determined over a large number of timepoints, which could help us reveal the underlying mechanism of hormesis. We present the results of a dose-time-response study on hormesis using five antibacterial chemicals on the bioluminescence of *Aliivibrio fischeri*, measuring expression of protein mRNA based on quorum sensing, simulating bioluminescent reaction and analyzing toxic actions of test chemicals. The findings show dose-time-dependent responses conforming to the hormetic dose-response model, while revealing unique response dynamics between agent induced stimulatory and inhibitory effects within bacterial growth

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phase dynamics. These dynamic dose-time features reveal a type of biological seesaw model that integrates stimulatory and inhibitory responses within unique growth phase, dose and time features, which has faultlessly explained the time-dependent hormetic phenomenon induced by five antibacterial chemicals (characterized by low-dose stimulation and high-dose inhibition). This study offers advances in understanding cellular dynamics, the biological integration of diverse and opposing responses and their role in evolutionary adaptive strategies to chemicals, which can provide new insight into the mechanistic investigation of hormesis.

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1. Introduction

Hormesis is a dose-response relationship phenomenon characterized by low-dose stimulation and high-dose inhibition, which has a biphasic feature typically represented as a J-shaped or an inverted U-shaped curve (Calabrese and Baldwin, 2002; Stebbing, 1982). Compared with the traditional threshold and linear non-threshold models, hormesis is believed to be the better fundamental model to reflect the actual dose response at both high and low doses (Calabrese, 2005; Calabrese and Baldwin, 2003a; b). Although hormetic phenomena, especially the time-dependent ones, have been frequently reported in many studies on a broad range of organisms and across a wide range of chemicals (Calabrese, 2008; Calabrese and Baldwin, 1998), there is no unified mechanism for these phenomena.

The topic of mechanistic exploration of hormesis is part of the history of hormesis and spans well over one hundred years (Calabrese, 2015). During the early stages, two key mechanisms for hormesis were proposed: direct stimulation (Szabadi, 1977) and overcompensation stimulation (Calabrese, 2001; Stebbing, 1982). Since then, many researchers have provided mechanistic explanations for different hormetic phenomena based on the approaches of receptor/signaling pathways (Calabrese, 2013; Calabrese and Baldwin, 2001). However, through analyzing these possible mechanisms, we found that most studies did not address the influence of time on hormetic effects and the proposed mechanisms could only explain hormetic phenomena at a specific timepoint (i.e., usually optimized). Meanwhile, many studies isolated the stimulatory effects from the inhibitory effects and were unaware of an agent that could simultaneously induce stimulatory and inhibitory effects at the tested endpoint. Due to these shortcomings, the proposed mechanisms did not address the time-dependent dimension of the hormetic phenomena. In 1986, Palazzo and Paalzow found that the biphasic dose response of apomorphine to the heart rate of rats (a hormetic effect) might be a combination of tachycardia (a stimulatory effect) and bradycardia (an inhibitory effect) (Paalzow and Paalzow, 1986). Furthermore, in our previous research, the hormetic dose-response curve could be accounted for by a model, the function of which is the algebraic summation of two logistic functions representing stimulatory and inhibitory effects (depicted in Fig. S1) (Deng et al., 2012). These findings indicate the need to simultaneously assess the impact of stimulatory and inhibitory effects when investigating the mechanisms of hormetic phenomena.

The luminescent bacteria, *Aliivibrio fischeri* (*A. fischeri*) has been widely used as a classic model organism in toxicity tests because its bioluminescence, as the test endpoint, is sensitive to changes in the environment, is convenient, and allows rapid evaluation (Girotti et al., 2008). In recent years, the effects of hormetic phenomena on the bioluminescence of *A. fischeri* have been frequently reported for a broad range of chemical chemicals, such as persistent organic pollutants, heavy metals, ionic liquids, and macromolecular compounds (Christofi et al., 2002; Froehner et al., 2002; Fulladosa et al., 2005; Ranke et al., 2004; Shen et al., 2009). In addition, it has been established that quorum sensing (QS) in *A. fischeri* has a close relationship with the hormetic phenomena on bioluminescence (Deng et al., 2012; You et al., 2016) because the bioluminescence is regulated by the signaling pathway of QS (depicted in Fig. S2). Therefore, further evaluation of how chemicals and/or physical agents act on the QS system of *A. fischeri* to simultaneously induce stimulatory and inhibitory effects on bioluminescence may be an effective approach to explore the underlying mechanisms of hormetic phenomena.

In this study, sulfapyridine (SPY), trimethoprim (TMP), tetracycline hydrochloride (TH), benzofuran-3(2H)-one (B3O) and (Z-)-4-bromo-5- (bromomethylene)-2(5H)-furanone (C30) were selected as representatives of several types of antibacterial agents that have shown hormetic effects on the bioluminescence of *A. fischeri* in our preliminary experiments. The present study has the following goals: 1) to determine the toxic effects of these five antibacterial agents on the bioluminescence and growth of *A. fischeri*; 2) to investigate how these chemicals induce stimulatory and inhibitory effects on QS-based bioluminescence by measuring the expression of protein mRNA, simulating the bioluminescent reaction and analyzing the toxic actions of the test chemicals; 3) to explore whether the apparent hormetic response of bioluminescence is a result of simultaneous and integrative stimulatory and inhibitory effects and how these opposite effects vary with time, resulting in time-dependent hormesis; and 4) to provide an enhanced mechanistic evaluation to account for time-dependent hormesis.

2. Materials and methods

2.1. Chemicals and organism

Test chemicals were purchased from Sigma-Aldrich (St. Louis, MO, America) without further purification (purity $\geq$ 99%), and the details are shown in Table 1. The freeze-dried bioluminescent bacterium *A. fischeri* was obtained from the American Type Culture Collection (No. 7744), reconstituted, and maintained on agar slants at 4 °C. The bacteria (F3) were inoculated from agar slants into liquid culture medium. The bioluminescence and bacterial density curves of *A. fischeri* (depicted in Fig. S3) were determined by using non-transparent 96-well microplates (Corning, America) on a Luminoskan Ascent (Thermo Scientific, America) and transparent 96-well microplates (Corning, America) on an automatic growth curve analyzer (Bioscreen C MBR, America), respectively. 80 μL 2% NaCl (Sigma-Aldrich, St. Louis, MO, America) solution, 80 μL culture medium, and 40 μL readily prepared *A. fischeri* (approximately 5×10^4 cell mL^{-1}) were added into the well in order (triplicate). The relative light unit (RLU) and optical density (OD_{600}) values of *A. fischeri* were tested per hour for 24 h, at 22 ± 1 °C. The growth of *A. fischeri* in 0–24 h could be divided into three phases: the lag phase (0–9 h), the logarithmic phase (10–17 h), and the stationary

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