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Abrianna Elke CHAIRIL

Laboratory of Marine Environmental Science, Division of Animal and Marine Biosciences,
Department of Bioresource Sciences, Graduate School of Bioresource and Bioenvironmental
Sciences, Kyushu University

TAKAI, Yuki

Laboratory of Marine Environmental Science, Faculty of Agriculture, Kyushu University

KUROGI, Kaito

Laboratory of Regulation in Metabolism and Behavior, Division of Animal and Marine
Biosciences, Department of Bioresource Sciences, Graduate School of Bioresource and
Bioenvironmental Sciences, Kyushu University

YASUO, Shinobu

Laboratory of Regulation in Metabolism and Behavior, Faculty of Agriculture, Kyushu University

他

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Starvation-induced alterations in brain monoamines may contribute to enhanced tolerance to the harmful alga *Karenia mikimotoi* in the Java medaka *Oryzias javanicus*

Abrianna Elke CHAIRIL¹, Yuki TAKAI², Kaito KUROI³, Shinobu YASUO⁴,
Koki MUKAI¹, Yukihiro MATSUYAMA⁵, Yuji OSHIMA² and Yohei SHIMASAKI^{2*}

Laboratory of Marine Environmental Science, Faculty of Agriculture,
Kyushu University, Fukuoka 819–0395, Japan

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Marine harmful algal blooms (HABs) caused by the dinoflagellate *Karenia mikimotoi* frequently induce severe fish mortality through gill damage and respiratory dysfunction. While starvation is generally regarded as a physiological stressor, short-term fasting has been reported to enhance fish tolerance to acute HAB toxicity. In this study, we investigated the effects of temporary starvation on survival and brain monoaminergic responses in marine medaka (*Oryzias javanicus*) exposed to *K. mikimotoi*. Adult fish were assigned to either fed or 48-h starved conditions and subsequently exposed to *K. mikimotoi* (1.0×10^4 cells mL⁻¹). Survival analysis demonstrated that starved fish survived markedly longer than fed fish, with the onset of mortality delayed by approximately 75 min. To explore the neurochemical mechanisms underlying this enhanced tolerance, brain concentrations of dopamine (DA), serotonin (5-HT), norepinephrine (NE), epinephrine (E), and their metabolites were quantified using high-performance liquid chromatography with electrochemical detection. As a result of the experiment, starved fish consistently exhibited lower concentrations of all measured monoamines and their metabolites in the non-exposed groups compared with fed fish, with the effect being more pronounced in the dopaminergic system. This overall tendency suggests broad suppression of dopaminergic, serotonergic, and noradrenergic activities under starvation conditions. In contrast, exposure to *K. mikimotoi* tended to increase the concentrations of these monoamines and their metabolites. However, even after exposure, starved fish generally maintained lower levels than fed fish for several compounds. Collectively, these findings suggest that short-term starvation induces a hypometabolic neurophysiological state characterized by reduced locomotor and respiratory activity, thereby suppressing oxygen consumption and delaying mortality. The present study highlights the potential role of the neuro-metabolic axis in mediating fish resilience against HAB toxicity and provides new insights into the neurophysiological mechanisms underlying starvation-induced tolerance to acute environmental stress.

Key words: harmful algal bloom, *Karenia mikimotoi*, monoamine, *Oryzias javanicus*, starvation

INTRODUCTION

Protection of marine biological resources is necessary to secure food resources from sustainable fisheries but there are many factors that may contribute to damaging the resources and inducing undesired side effects towards economic activities. One such threat to the sta-

bility of marine resources is the increase in harmful algal bloom (HAB) occurrences. HAB species such as *Karenia mikimotoi* are known for causing mass mortalities in fish and shellfish species (Shi *et al.* 2012). These blooms have emerged in many regions including Japan (Honjo 1994; Yoshimatsu 2008), where they have resulted in cumulative economic losses of approximately 9 billion yen over the past 30 years (Miyake and Onitsuka 2025) due to the mass mortality of wild and farmed fish such as yellowtails and red sea breams. The ichthyotoxicity of *K. mikimotoi* is primarily attributed to direct physical contact and the release of reactive oxygen species (ROS) or cytotoxic exudates, which induce severe damage to the gill epithelium (Chairil *et al.* 2024; Mooney *et al.* 2009; Yamasaki *et al.* 2004). This localized tissue damage compromises osmoregulation and gas exchange, ultimately leading to respiratory distress, hypoxia, and death. Consequently, understanding physiological and behavioral responses that might delay or mitigate this rapid toxicity is of critical importance.

While environmental stressors typically exacerbate the vulnerability of fish to toxins, short-term starvation has emerged as a counterintuitive mitigation strategy against acute ichthyotoxicity. Fasting induces a widespread physiological shift in fish, characterized by a transition to a hypometabolic state to conserve energy

¹ Formerly at Laboratory of Marine Environmental Science, Division of Animal and Marine Biosciences, Department of Bioresource Sciences, Graduate School of Bioresource and Bioenvironmental Sciences, Kyushu University, 744 Motooka, Nishi-ku, Fukuoka City, 819–0395, Japan

² Laboratory of Marine Environmental Science, Faculty of Agriculture, Kyushu University, 744 Motooka, Nishi-ku, Fukuoka City, 819–0395, Japan

³ Formerly at Laboratory of Regulation in Metabolism and Behavior, Division of Animal and Marine Biosciences, Department of Bioresource Sciences, Graduate School of Bioresource and Bioenvironmental Sciences, Kyushu University, 744 Motooka, Nishi-ku, Fukuoka City, 819–0395, Japan

⁴ Laboratory of Regulation in Metabolism and Behavior, Faculty of Agriculture, Kyushu University, 744 Motooka, Nishi-ku, Fukuoka City, 819–0395, Japan

⁵ Fisheries Technology Institute, Japan Fisheries Research and Education Agency, 1551–8 Taira-cho, Nagasaki, 851–2213, Japan

* Corresponding author (E-mail: simasaki@agr.kyushu-u.ac.jp)

reserves (Navarro and Gutiérrez 1995). This metabolic depression is often accompanied by reduced spontaneous locomotor activity and a lowered baseline respiratory rate. As *K. mikimotoi* toxicity is highly dependent on the rate of water flow over the gills, a reduction in gill ventilation driven by the hypometabolic state of starvation can theoretically reduce the total volume of toxic cells and their exudates from encountering the gill surface. This may ultimately prolong the survival of fish during *K. mikimotoi* bloom events.

Despite these observed survival benefits, the underlying neurochemical mechanisms that drive this protective hypometabolic state during starvation remain poorly understood. Central monoaminergic systems—specifically dopamine (DA), serotonin (5-HT), and norepinephrine (NE)—are the primary neuroendocrine regulators of behavior, arousal, and metabolic expenditure in teleosts (Winberg and Nilsson 1993). For instance, the dopaminergic and serotonergic systems strongly regulate locomotor drive, while the adrenergic system dictates cardiovascular and respiratory responses to stress (Clements *et al.* 2002). As such, analyzing the production of these neurotransmitters is essential for elucidating how the central nervous system orchestrates the whole-body metabolic depression that may contribute to survival under acute environmental stress.

To bridge this gap, the present study investigates the central monoaminergic responses in fed and starved marine medaka (*Oryzias javanicus*) under baseline conditions and during exposure to *K. mikimotoi*. By quantifying the levels of primary monoamines and their active metabolites (such as DOPAC and HVA), this research aims to elucidate the neurochemical pathways that suppress locomotor and respiratory activity during fasting. Ultimately, this study highlights the importance of the neuro-metabolic axis in mediating environmental resilience, providing a mechanistic explanation for the extended survival of starved fish during harmful dinoflagellate blooms.

MATERIALS AND METHODS

Fish culture

Adult *Oryzias javanicus* (~6 months old) were maintained in glass tanks. The water temperature was kept at $25 \pm 1^\circ\text{C}$ and a salinity of 35 with an aerating filter system in each tank. The fish were maintained on a 16:8-h light:dark cycle. *Artemia* nauplii amounting to 2% of Java medaka body weight were given twice daily at 09:00 and 18:00 JST. The fish tanks were cleaned by replacing half of the water every two weeks.

Algae culture

A non-axenic strain of *K. mikimotoi* isolated from Omura Bay (Nagasaki, Japan) was obtained from the Seikai National Fisheries Research Institute. The *K. mikimotoi* cells were kept in culture flasks suspended in modified SWM-3 medium (Yamasaki *et al.* 2007) at a pH of 7.9 and a salinity of 30. The cells were maintained at 20°C and an irradiance of $100 \pm 10 \mu\text{mol photons m}^{-2} \text{ s}^{-1}$

provided on a 12:12-h light:dark cycle.

Feeding and Fasting treatments

Adult Java medaka were divided into four groups: fed-control (FC) and fed-*K. mikimotoi* exposure (FE), starved-control (SC) and starved-*K. mikimotoi* exposure (SE). *Artemia* nauplii amounting to 2% of Java medaka body weight were given twice daily at 09:00 and 18:00 JST to the feeding group. Starvation and feeding treatments were conducted for 48 hours prior to the start of the exposure to *K. mikimotoi* cultures.

Survival analysis

Phenotypically male adult Java medaka ($n = 7$) at the age of 6-months post-hatch were taken and transferred into a 1000 mL beaker filled with newly concocted artificial sea water at a salinity of 35 acclimated to 25°C . The fish were left to acclimatize at the exposure locations for an hour prior to the start of the exposure experiment.

The cultured *K. mikimotoi* cell suspensions grown to the stationary phase were sampled and counted using a microscope. From the obtained density value, the necessary volume of algal cultures to be used in the exposure groups was calculated to achieve a final density of 1.0×10^4 cells mL^{-1} of *K. mikimotoi* which is a reduced amount from the density required to achieve 100% mortality rate in adult marine medaka *Oryzias melastigma* within 60 minutes (Kwok *et al.* 2021). The cultures were added into artificial sea water to a total of 1,000 mL suspension in the observation tank and were left to acclimatize to the test area for an hour. Equal volumes of modified SWM-3 medium were used in place of the algal cultures for the non-exposure groups.

The observation was conducted for 180 minutes with the starting time of the observation noted. Mortality of the Java medaka was observed and when a fish showed no movement after 30 seconds of mild agitations, it is then considered dead in which the time of death was recorded with the body removed from the test area.

Brain monoamine analysis

Monoamine concentrations of dopamine (DA) and its metabolites—3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA); serotonin (5-HT) and its metabolite—5-hydroxyindoleacetic acid (5-HIAA); and norepinephrine (NE) and its metabolite—3-methoxy-4-hydroxyphenylglycol (MHPG) in whole Java medaka brains post-survival testing were assayed as described by Qiu *et al.* (2020) and Kurogi *et al.* (2023). This assay was performed using high-performance liquid chromatography electrochemical detector Stand-Alone System (HTEC-510; Eicom Co. Ltd., Kyoto, Japan) with octadecyl silane column (SC-50DS, Eicom). Brain samples were homogenized in 0.2 mol L^{-1} of perchloric acid solution through sonication, which were then left to incubate on ice for 30 minutes to deproteinize. The mixture was then centrifuged to separate the tissue debris and the supernatants for 15 minutes at 4°C using $20,000 \times g$ centrifugal power. $0.2 \mu\text{m}$ hydrophilic polytetrafluoroethylene filters (Millipore, Bedford, MA, USA)

were used to additionally remove excess debris in the supernatant from the tissues. A mobile phase solution was prepared from a mixture of 0.1 M citric acid, 0.1 M sodium acetate, 100 mg mL⁻¹ sodium 1-octane sulfonate, 5 mg mL⁻¹ ethylenediaminetetraacetic acid (EDTA) and methanol, and infused at a flow rate of 0.5 mL min⁻¹. An external standard solution for each monoamine at a concentration of 0.1 ng mL⁻¹ was used as a reference for the peak location and retention time for the homogenates. Each individual monoamine was detected using the electrochemical detector integrated in the aforementioned HTEC-510 system with an applied potential of 700–750 mV and a detection limit of 0.1 pg per sample, and chromatographic data were processed using the EPC-500 data processor (Eicom). The calculated monoamine concentrations were expressed as pg mg⁻¹ of tissue.

Statistical analysis

Survival curves were analyzed using the Kaplan–Meier method, and differences among groups were evaluated using the log-rank test followed by Benjamini–Hochberg correction for multiple comparisons.

Monoamine and their metabolite concentrations are presented as mean $\pm$ standard deviation (SD). Homogeneity of variance was assessed using Levene's test prior to statistical comparisons. If the assumption of homogeneity was satisfied, differences among groups were analyzed using Student's *t*-test with Bonferroni correction for multiple comparisons. When the assumption of homogeneity was not met, nonparametric analyses were performed using the Wilcoxon rank-sum test followed by Dunn's post hoc test with *P*-value adjustment.

All statistical analyses were performed using RStudio version 2022.12.0 (Posit, PBC., Massachusetts, USA) running on R version 4.2.1 (Team 2008). Statistical significance was accepted at *P* < 0.05.

RESULTS

Survival analysis

The survival experiment showed a clear delay in the time of deaths between the fed group and the starved group (Fig. 1). The first death in the fed-exposure group and starved-exposure group was at around 60 minutes and 135 minutes post-exposure, respectively. Pairwise comparisons using Log-Rank test with Benjamini–Hochberg correction indicated a significant difference (*P* < 0.01) between the survival rates of the two exposure groups, along with their respective controls.

Brain monoamine analysis

To assess the neurochemical effects of *K. mikimotoi* exposure on Java medaka under different feeding programs, we quantified the levels of monoamines DA, 5-HT, NE, E, and their respective metabolites (Fig. 2).

Effects on the Dopaminergic System

Dopamine (DA) and its metabolites (DOPAC and HVA) showed the most pronounced variation among

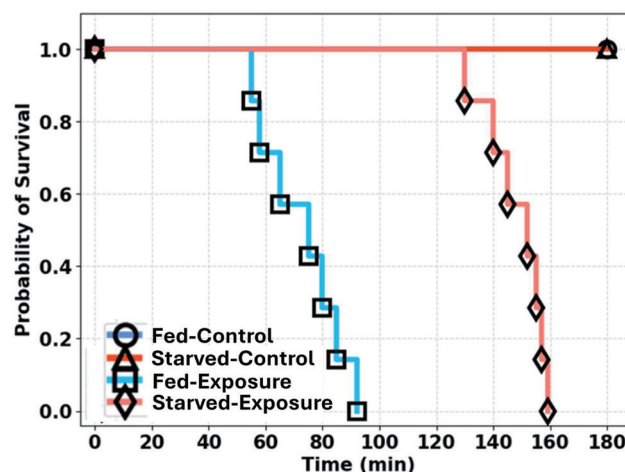


Fig. 1. Kaplan–Meier survival curves of adult Java medaka exposed to 1.0×10^4 cells mL⁻¹ of *Karenia mikimotoi* and non-exposed control groups (*n* = 7). A significant difference in survival was detected between the Fed-Exposure and Starved-Exposure groups using the log-rank test (*P* < 0.01).

groups, as reflected by significant changes in its metabolites. Starvation was associated with reduced DA and its metabolites, with the SC group exhibiting the lowest HVA levels (0.019 ± 0.011 pg mg⁻¹) compared with the FC group (0.104 ± 0.023 pg mg⁻¹). In contrast, exposure to *K. mikimotoi* in the FE group resulted in elevated DOPAC (0.375 ± 0.033 pg mg⁻¹) and HVA (0.155 ± 0.006 pg mg⁻¹), indicating an enhanced dopamine-related response.

Effects on the Serotonergic System

Analysis of 5-HT and its primary metabolite, 5-HIAA, revealed a similar trend. The SC group displayed the lowest concentrations of both 5-HT (0.109 pg mg⁻¹) and 5-HIAA (0.133 pg mg⁻¹). The FE group exhibited the most pronounced elevation in 5-HT levels, with mean 5-HT levels of 0.328 pg mg⁻¹ and 5-HIAA levels of 0.394 pg mg⁻¹. The SE and FC groups showed intermediate levels that were relatively comparable to one another but elevated compared to the SC baseline.

Effects on the Noradrenergic and Adrenergic Systems

Norepinephrine (NE), E, and the NE metabolite MHPG were quantified to assess the impact of starvation on the adrenergic/noradrenergic system. Norepinephrine levels were highly responsive to the experimental conditions, rising from a mean of 0.592 pg mg⁻¹ in the SC group to 1.415 pg mg⁻¹ in the FE group. 3-methoxy-4-hydroxyphenylglycol (MHPG) levels followed a corresponding trajectory, nearly doubling from the SC group (0.494 pg mg⁻¹) to the FC (0.970 pg mg⁻¹) and FE (0.939 pg mg⁻¹) groups. Epinephrine (E) levels showed the most modest fluctuations among the monoamines tested, though they still trended upward from the SC (0.335 pg mg⁻¹) to the FE (0.505 pg mg⁻¹) group.

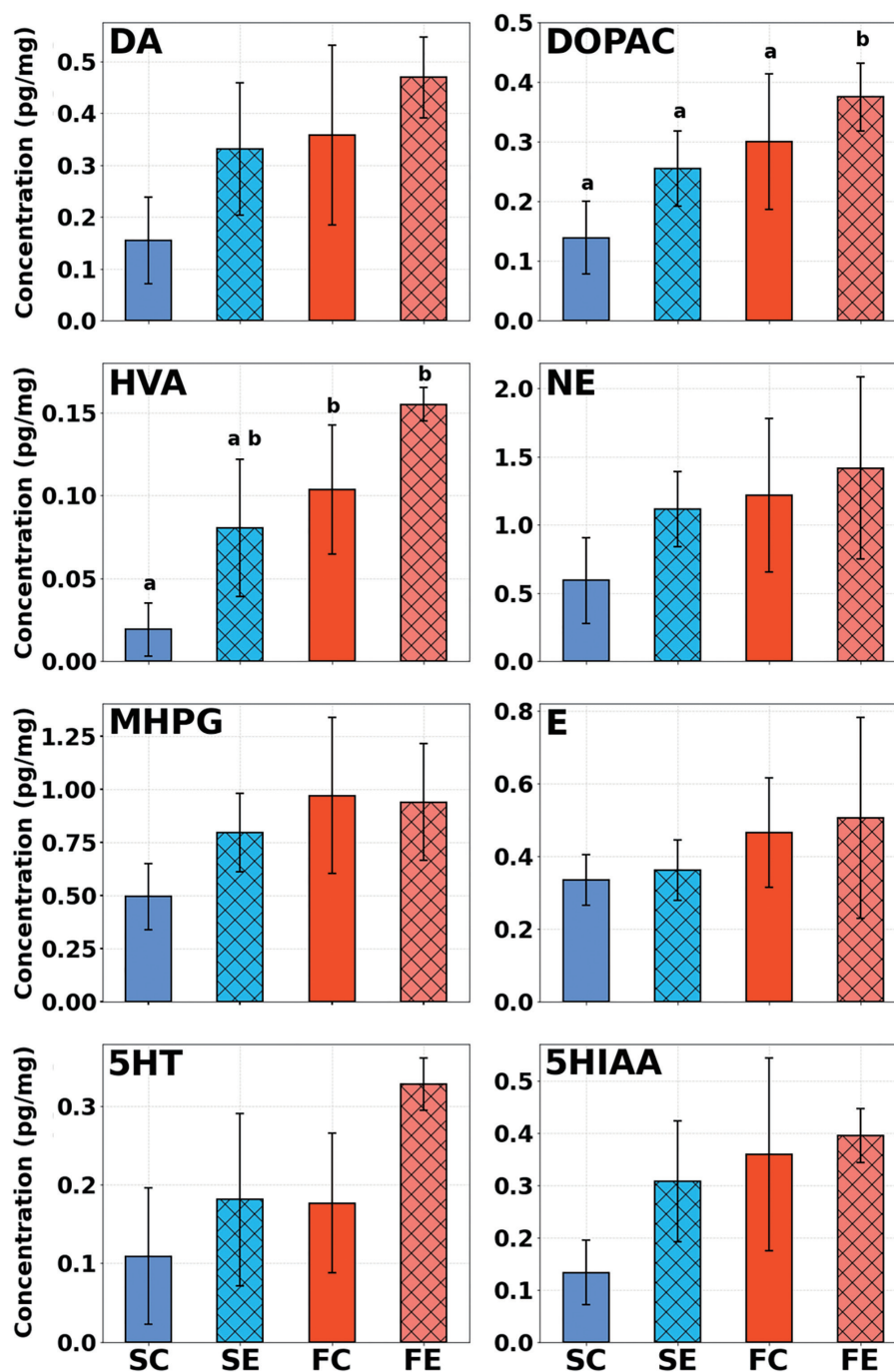


Fig. 2. Monoamine and metabolite concentrations in the brains of fed and starved Java medaka exposed to 0 or 1.0×10^4 cells mL^{-1} of *Karenia mikimotoi*. SC, SE, FC, and FE represent Starved-Control, Starved-Exposure, Fed-Control, and Fed-Exposure groups, respectively. "Exposure" indicates exposure to *Karenia mikimotoi*. DA, DOPAC, HVA, NE, MHPG, E, 5-HT, and 5-HIAA indicate dopamine, 3,4-dihydroxyphenylacetic acid, homovanillic acid, norepinephrine, 3-methoxy-4-hydroxyphenylglycol, epinephrine, serotonin, and 5-hydroxyindoleacetic acid, respectively. Different letters above bars indicate significant differences among groups ($P < 0.05$; all groups: $N = 4$, except starved control: $N = 3$); groups sharing the same letter are not significantly different, and no letters indicate no significant differences among groups.

DISCUSSION

The present study investigated the effects of short-term starvation on monoamine production in *O. javanicus*, and how this physiological shift influences survival during exposure to the toxic dinoflagellate *K. mikimotoi*.

Our findings strongly suggest a widespread down-regulation of monoaminergic activity in response to food deprivation. Across the dopaminergic, serotonergic, and noradrenergic/adrenergic systems, the starved groups consistently exhibited lower concentrations of both primary neurotransmitters and their metabolites compared

to the fed groups. Crucially, this neurochemical suppression coincided with a significant increase in survival time; starved *O. javanicus* survived approximately one hour longer than their fed counterparts when exposed to *K. mikimotoi*. These results suggest that starvation induces a neurochemically driven hypometabolic state that acts as a protective mitigation strategy against acute ichthyotoxicity (Navarro and Gutiérrez 1995).

Metabolic Depression and Mitigation of Toxic Effects

Norepinephrine (NE) and epinephrine (E) are primary drivers of physiological arousal in teleosts, mediating cardiovascular output, gill ventilation rates, and oxygen consumption during stress (Perry and Bernier 1999). The chronic metabolic stress of starvation in this study resulted in significantly lower baseline levels of these catecholamines and the NE metabolite MHPG. By dampening the adrenergic drive, starved *O. javanicus* may have experienced a marked reduction in overall metabolic rate and respiration. The ichthyotoxicity of *K. mikimotoi* is heavily dependent on the physical interaction between the toxic cells or reactive oxygen species (ROS) and the gill epithelium, which induces severe localized damage and compromises gas exchange (Mooney *et al.* 2009; Yamasaki *et al.* 2004). Because this toxicity is dependent on exposure volume, a slower ventilation rate—driven by suppressed adrenergic tone—could effectively reduce the volume of toxic water passing over the gills. Consequently, this suppression may serve as a defense mechanism, delaying the accumulation of gill damage and extending survival time during the exposure window.

Dopaminergic System and Locomotor Activity

Dopamine (DA) plays a critical role in regulating locomotor activity, arousal, and energy expenditure in teleosts (Clements *et al.* 2002; Messias *et al.* 2016). The marked reduction in DA, alongside the statistically significant decreases in its primary metabolites DOPAC and HVA, points to a profound systemic suppression of dopaminergic pathways in the starved groups. Because DOPAC and HVA are generated during the breakdown of dopamine, their significant reduction specifically indicates a severe drop in DA level and synaptic release. Active swimming requires substantial oxygen and further drives up gill ventilation rates; therefore, downregulating DA utilization may represent a highly effective adaptive strategy to reduce spontaneous locomotor activity. Exposure to *K. mikimotoi* is known to induce abnormal, high-energy swimming behaviors in teleosts, often due to physical gill irritation (Chairil *et al.* 2024; Niu *et al.* 2021). By minimizing baseline movement through dopaminergic suppression, starved fish may conserve energy reserves and potentially reduce encounters with *K. mikimotoi* cells in the water column. The statistically significant blunting of dopaminergic synthesis acts synergistically with the suppressed adrenergic system to limit overall toxin exposure to the gills.

Serotonergic System and Behavioral Shifts

The serotonergic system is deeply integrated into the regulation of stress, aggression, and metabolic arousal (Winberg and Nilsson, 1993). The significant decrease in central 5-HT and its metabolite 5-HIAA observed in the starved groups further supports a systemic shift toward energy conservation. While 5-HT often acts to suppress appetite in fish, its downregulation here may also be tied to a generalized dampening of the stress-arousal axis. By reducing serotonergic production, the fish may be suppressing energetically costly panic or escape behaviors that would otherwise be triggered by the noxious stimulus of the red tide organism, further preventing dangerous spikes in gill ventilation.

CONCLUSION

In conclusion, short-term starvation in *O. javanicus* triggers a coordinated downregulation of major monoaminergic pathways. Rather than simply reflecting a deficit in neurotransmitter precursors, this suppression of DA, 5HT, and NE/E effectively induces a hypometabolic state. This reduction in baseline locomotor activity and particularly gill ventilation, may limit the uptake and localized damage of *K. mikimotoi* ichthyotoxins, ultimately extending survival time. These findings highlight the profound interplay between nutritional state, neurochemistry, and environmental stress resilience in marine medaka.

AUTHOR CONTRIBUTIONS

A. E. Chairil designed the study, performed all experiments, analyzed the data and wrote the paper. Y. Takai designed the study, analyzed the survival data and supervised the work. K. Kurogi and S. Yasuo performed the monoamine analysis. K. Mukai designed the study. Y. Matsuyama provided resources and supervised the work. Y. Oshima supervised the work and provided facilities. Y. Shimasaki designed the study, supervised the work. All authors assisted in editing of the manuscript and approved the final version.

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