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Impact of Biogenic Amines on the Growth of Green Microalgae

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Abstract:

Background: The goal of this research project was to test various neuroactive amines in the capacity of growth stimulators/accelerators of the green microalgae *Scenedesmus quadricauda* and *Chlorella vulgaris* that have much biotechnological potential because they can be used for producing drugs, food ingredients, cosmetics, and biofuel. The issue of the ecological role of the biogenic amines in terms of interspecies communication in aqueous ecosystems was also addressed in this work.

Methods: *S. quadricauda* strain GEHD and *C. vulgaris* strain ALP were cultivated in the light with constant aeration at 24°C in a minerals-containing medium. Experimental systems contained 1, 10 or 100 µM of dopamine hydrochloride, histamine hydrochloride, norepinephrine hydrochloride, or serotonin hydrochloride that were added at inoculation as freshly prepared aqueous solutions. Algal cells were counted using a light microscope, and their number in 1 mL of culture was calculated. The culture liquid and sonicated biomass of *S. quadricauda* and *C. vulgaris* were tested for the presence of endogenous amines using high-performance liquid chromatography (HPLC) with an amperometric detector.

Results: The biogenic amines serotonin, norepinephrine, dopamine, and histamine significantly stimulated the growth of *S. quadricauda*, at concentrations of 1 and/or 10 µM but not 100 µM. Histamine was the most efficient stimulator, causing an average 65% increase in biomass accumulation at the end of the cultivation period. The effects of serotonin, dopamine and histamine on *C. vulgaris* were reported in our previous publication [1], but this work contains the results of our experiments with the previously untested norepinephrine that slightly stimulated the growth of *C. vulgaris*. HPLC analysis failed to reveal any endogenous amines in the culture liquid and biomass of both microalgae.

Conclusions: Since biogenic amines stimulate the growth of the microalgae *S. quadricauda* and *C. vulgaris* but are not synthesized by them, we suggest that the algae normally respond to amines produced by other components of aqueous ecosystems, including zooplankton and fish that are known to release significant amounts of biogenic amines into the environment. The data obtained hold some promise with regard to developing a relatively economical technique of boosting algal biomass production.

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INTRODUCTION

Green microalgae are important representatives of the phytoplankton of fresh-water ecosystems. They are involved in the trophic chains of aquatic ecosystems. For instance, crustaceans and other water invertebrates feed on them. From the perspective of the *Journal of Pharmacy and Nutrition Science*, it is of paramount importance that microalgae find applications in healthcare, cosmetics, and the food industry; they have much potential as economical biofuels. This is the reason why research aimed at enhancing the growth rate and biomass production by microalgae is of so much practical interest. Our previous research project addressed the idea of stimulating/accelerating the growth of the industrially and environmentally important microalga *Chlorella vulgaris* with the neuroactive biogenic amines serotonin, dopamine, and histamine; the data obtained indicated that, indeed, these amines increase the growth rate of the *C. vulgaris* culture, histamine being the most powerful growth stimulator [1]. The work cited dealt with the ecological and environmental implications of these results since algae communicate with other ecosystem components that actively release biogenic amines into the environment. This is characteristic of aqueous bacteria [2], coastal higher plants [3, 4], and invertebrates exemplified by the zooplankton [5].

In the present work, the published data [1] on *Chlorella* (and the additional data on the effect of the previously untested norepinephrine on this alga, which are included in this work) are compared to the new results obtained with another biotechnologically and environmentally useful algal species, *Scenedesmus quadricauda*. Taxonomically, this species belongs to the family *Scenedesmaceae* and the order *Sphaeropleales*

Interestingly, *Scenedesmus* produces a wide spectrum of biologically active substances, including (i) antioxidants and UV protectors such as asthaxanthin, β -carotene, mycosporins, and sporopollenin; (ii) vitamins B, C, and E; (iii) chlorophylls *a*, *b*, and *c* employed as food colorants along with other industrial applications; and (iv) antimicrobial agents exemplified by fatty acids [6].

To re-emphasize, this work is aimed at evaluating the capacity of biogenic amines to stimulate/accelerate the growth of *Scenedesmus quadricauda*. Biogenic amines function, in the animal organism, as neurotransmitters that transfer impulses between nervous cells. Many of

them operate as signals and/or effectors in various kingdoms of life including plants (reviewed, [4]) and pro- and eukaryotic microorganisms [2]. The impact of biogenic amines on the microalga *Scenedesmus* is still unexplored; some research has already been conducted with other algal species, including our earlier work with *Chlorella* recently published in JPANS [1].

MATERIALS AND METHODS

Investigating the Impact of Biogenic Amines on the Growth of Microalgae

The strains *Scenedesmus quadricauda* GEHD and, in a limited number of experiments, *Chlorella vulgaris* ALP were cultivated in the light with constant aeration at 24°C in the medium with the following composition (g/L): KNO₃ 2.5; MgSO₄ x 7H₂O 1.25; KH₂PO₄ 0.625; FeSO₄ x 7H₂O 0.003; ethylene diamine tetraacetate 0.185; microelement mixture 1 mL per 1 L (pH 6.0). The microelement mixture composition was as follows (g/L): H₃BO₃: 2.86; MnCl₂ x 4H₂O: 1.81; ZnSO₄ x 7H₂O: 0.222; MoO₃ 176.4 mg/10 L; NH₄VO₃: 229.6 mg/10 L; CuSO₄ x 5H₂O: 0.01 mg/L; Co(NO₃)₂ x 4H₂O: 0.146; KJ: 0.083; NaWO₄ x H₂O: 0.033; NiSO₄(NH₄)SO₄ x 6H₂O: 0.198. An actively growing culture was used as inoculum. It was diluted by the medium to a final cell concentration of 0.59×10⁶ cells/cm³ in *S. quadricauda* and 1.4×10⁶ cells/cm³ in *C. vulgaris*, which corresponded to an optical density (OD) of 0.10±0.1 in *S. quadricauda* and 0.12±0.1 in *C. vulgaris*, respectively, at $\lambda = 540$ nm. The culture was grown until the OD₅₄₀ value reached a plateau level, which corresponded to day 7 of cultivation in *S. quadricauda* and to day 4 in *C. vulgaris*. The selected time points (1, 2, 4, and 7 days for *S. quadricauda* and 1, 2, 3, and 4 days of cultivation for *C. vulgaris*) corresponded to the lag phase, the early exponential phase, the late exponential phase, and the stationary phase, respectively.

The experimental systems (in which the algae grew in the presence of biogenic amines) contained 1, 10 or 100 μ M of dopamine hydrochloride, histamine hydrochloride, norepinephrine hydrochloride, or serotonin hydrochloride that were added at inoculation as freshly prepared aqueous solutions; the control system (in which the algae grew without biogenic amines) was supplemented with an equal volume of water at inoculation. All neurochemicals were analytic grade, purchased from the Sigma company (USA). Algal cells were counted using a light microscope, and their number was calculated for a culture volume of

1 mL. In some experiments, we used a calibration curve in order to estimate the cell number in the cultures based on the optical density values at 540 nm. OD values were measured using a LOMO spectrophotometer (Russia). 4-5 independent repeats of each experiment were performed; the mean values and the standard deviations were calculated using statistical techniques.

Measuring the Concentrations of Endogenous Amines

Endogenous amines were determined in samples of the culture liquid and the sonicated biomass of *S. quadricauda* and *C. vulgaris*. The cultures were harvested during the stationary growth phase (day 7 of cultivation with *S. quadricauda* and day 4 with *C. vulgaris*, respectively). Samples of biomass were cooled to 0°C and disintegrated ultrasonically (22 kHz, 7-8 min). The culture liquid and the supernatant obtained by centrifugation (8,000 g, 10 min) of disintegrated algal cells were acidified to pH 1 with hydrochloric acid and stored at -10 °C.

The biogenic amines dopamine, norepinephrine, and serotonin, as well as the catecholamine precursor 2,3-dihydrophenylalanine (DOPA) were separated by high-performance liquid chromatography (HPLC) with an amperometric detection system [7]. A LC-304T chromatographer (BAS, West Lafayette, USA) with a Rheodyne 7125 injector was used; the volume of the loop used for applying samples was 20 µl. The tested biogenic amines were separated on a reverse-phase ReproSil-Pur column (ODS-3, 4x100 mm, 3 µ; Dr. Majsch GMBH, Elsico, Moscow). A PM-80 pump (BAS, USA) was used; the elution rate of the mobile phase was 1.0 ml/min at a pressure of 200 atm. The mobile phase contained 0.1 M citrate-phosphate buffer with 1.1 mM octanesulfonic acid, 0.1 mM EDTA, and 9% acetonitrile (pH 3.0). The measurements were carried out using an LC-4B electrochemical detector (BAS, USA) with a glass-carbon electrode (+0.85 V) against an Ag/AgCl reference electrode. The samples were

scanned with the Multichrome 1.5 (Ampersand) hardware-software system. All reagents used for the assay were of analytical grade. The chromatographer was calibrated using a mixture of the tested biogenic amines; the concentrations of all these substances were 0.5 µM. The amine concentrations contained in the samples were calculated by the internal standard method that is based on determining the ratio between the peak area in the standard mixture and that in the samples [13].

RESULTS

The growth dynamics of *Scendesmus quadricauda* cultures in the presence of the biogenic amines serotonin, histamine, dopamine, and norepinephrine, or without them (control) is displayed in Tables 1-4. The selected time points, as mentioned in the Materials and Methods section, corresponded to the lag phase, the early exponential phase, the late exponential phase, and the stationary phase, respectively. The data on each biogenic amine except norepinephrine were compared with those obtained in the previous work [1] on *Chlorella vulgaris*.

Effect of Serotonin on the Growth of the *S. quadricauda* Culture

Serotonin at concentrations of 1 and 10 µM brought about an approximately 30% increase in *S. quadricauda* biomass yield, according to the data on the cell number in the algal culture towards the end of the culture's growth period (day 7 of cultivation, Table 1). Stimulation was not caused by 100 µM serotonin. For comparison, serotonin increased the biomass yield of *C. vulgaris* only at a concentration of 10 µM, and this stimulation was less significant (~12% of the control).

Effect of Histamine on the Growth of the *S. quadricauda* Culture

Histamine was the strongest growth stimulator among the biogenic amines at all tested concentrations, and the maximum (~65%) growth stimulation was achieved

Table 1: Growth dynamics of *S. quadricauda* cultures (cell numbers per 1 mLx10⁻⁶) cultivated with or without serotonin. Note: The Table contains the averaged results of 4-5 repeats; standard deviations are given

Days of cultivation	Control	1 µM serotonin	10 µM serotonin	100 µM serotonin
0 (inoculation)	0.59	0.59	0.59	0.59
1	0.82±0.1	0.94±0.1	0.94±0.1	0.82±0.1
2	1.7±0.2	2.3±0.3	2.4±0.3	1.9±0.2
4	4.5±0.4	5.6±0.5	5.6±0.5	4.1±0.3
7	6.4±0.5	8.2±0.6	8.2±0.5	6.1±0.4

Table 2: Growth dynamics of *S. quadricauda* cultures (cell numbers per 1 mLx10⁻⁶) cultivated with or without histamine. Note: The Table contains the averaged results of 4-5 repeats; standard deviations are given

Days of cultivation	Control	1 μ M histamine	10 μ M histamine	100 μ M histamine
0 (inoculation)	0.59	0.59	0.59	0.59
1	0.94 \pm 0.1	1.1 \pm 0.2	1.1 \pm 0.2	0.94 \pm 0.1
2	1.8 \pm 0.2	2.6 \pm 0.3	2.6 \pm 0.3	2.2 \pm 0.3
4	4.8 \pm 0.5	7.6 \pm 0.5	7.1 \pm 0.4	6.5 \pm 0.4
7	6.4 \pm 0.5	8.8 \pm 0.6	10.6 \pm 0.6	8.8 \pm 0.6

at a concentration of 10 μ M. The increase in growth rate already manifested itself at early growth stages (Table 2) but it was especially significant towards the end of the growth period. A similar effect was produced by histamine on *C. vulgaris* but, unlike *S. quadricauda*, *C. vulgaris* did not increase its growth rate with the highest tested histamine concentration (100 μ M) that even was inhibitory to the *Chlorella* culture [1].

Effect of Dopamine on the Growth of the *S. quadricauda* Culture

As shown in Table 3, dopamine significantly increased the *S. quadricauda* biomass yield. The averaged stimulatory effect at dopamine concentrations of 1 and 10 μ M was 36% and 45% of the control, respectively, on day 7 of cultivation. In the previously published work, dopamine exerted a stimulatory influence on *C. vulgaris*. However, dopamine only increased the cell numbers in its culture at the early stages of its growth, i.e., dopamine accelerated *C. vulgaris* growth rather than increased the final biomass yield [1]. No growth

increase was observed at the highest tested concentration (100 μ M) in both algae; presumably, another, inhibitory, effect caused by this dopamine concentration overrode the accelerating effect.

Effect of Norepinephrine on the Growth of the *S. quadricauda* Culture

Norepinephrine was expected to behave like dopamine since the two compounds are structurally similar (norepinephrine only has an extra hydroxy group). Norepinephrine stimulated the growth of *S. quadricauda* by ~30% at concentrations of 1 and 10 μ M; 100 μ M norepinephrine failed to exert any effect (Table 4). Since norepinephrine was not tested in the published work with *C. vulgaris*, we conducted this study in terms of this research project.

Effect of Norepinephrine on the Growth of the *C. vulgaris* Culture

As shown in Table 5, norepinephrine (1 μ M) increased the biomass yield by 13%, compared to the control

Table 3: Growth dynamics of *S. quadricauda* cultures (cell numbers per 1 mLx10⁻⁶) cultivated with or without dopamine. Note: The Table contains the averaged results of 4-5 repeats; standard deviations are given

Days of cultivation	Control	1 μ M dopamine	10 μ M dopamine	100 μ M dopamine
0 (inoculation)	0.59	0.59	0.59	0.59
1	0.88 \pm 0.1	0.88 \pm 0.1	1.0 \pm 0.1	0.82 \pm 0.1
2	1.8 \pm 0.2	2.2 \pm 0.2	2.3 \pm 0.2	1.8 \pm 0.2
4	4.7 \pm 0.4	5.6 \pm 0.4	6.5 \pm 0.4	4.7 \pm 0.5
7	6.5 \pm 0.3	8.8 \pm 0.5	9.4 \pm 0.5	6.2 \pm 0.3

Table 4: Growth dynamics of *S. quadricauda* cultures (cell numbers per 1 mLx10⁻⁶) cultivated with or without norepinephrine. Note: The Table contains the averaged results of 4-5 repeats; standard deviations are given

Days of cultivation	Control	1 μ M norepinephrine	10 μ M norepinephrine	100 μ M norepinephrine
0 (inoculation)	0.59	0.59	0.59	0.59
1	0.82 \pm 0.1	0.88 \pm 0.1	0.94 \pm 0.1	0.82 \pm 0.1
2	1.7 \pm 0.2	1.8 \pm 0.2	2.1 \pm 0.2	1.8 \pm 0.2
4	4.5 \pm 0.4	4.7 \pm 0.4	5.6 \pm 0.4	4.7 \pm 0.4
7	6.2 \pm 0.4	7.1 \pm 0.5	7.6 \pm 0.5	6.5 \pm 0.4

Table 5: Growth dynamics of *C. vulgaris* cultures (cell numbers per 1 mLx10⁻⁶) cultivated with or without norepinephrine. Note: The Table contains the averaged results of 4-5 repeats; standard deviations are given

Days of cultivation	Control	1 μ M norepinephrine	10 μ M norepinephrine	100 μ M norepinephrine
0 (inoculation)	1.4	1.4	1.4	1.4
1	4.3 \pm 0.3	4.9 \pm 0.4	5.4 \pm 0.4	4.3 \pm 0.3
2	8.5 \pm 0.5	11.0 \pm 0.6	11.7 \pm 0.6	9.8 \pm 0.5
4	11.2 \pm 0.6	14.0 \pm 0.7	13.7 \pm 0.7	13.7 \pm 0.7
7	17.5 \pm 0.7	19.8 \pm 0.8	18.7 \pm 0.8	22 \pm 1

culture, by day 4 of cultivation, i.e. by the onset of the stationary growth phase. The stimulatory effect was more significant (~37%) at the beginning of the exponential phase (day 2 of cultivation). Like dopamine, norepinephrine tended to accelerate the growth of *C. vulgaris* rather than increase the final biomass yield. In contrast, both neurochemicals exerted a true stimulatory effect on *S. quadricauda* in terms of biomass yield.

The above findings raised the issue of the purpose of the impact of the tested biogenic amines on the growth of microalgal cultures. A typical pattern in a large number of other organisms, exemplified by many pro- and eukaryotic microorganisms, is that neurochemicals including biogenic amines (i) exert a stimulatory effect on these organisms and (ii) are produced by them and frequently released into the culture liquid [2]. Therefore, such neurochemicals behave as autoregulators [8], i.e., they specifically influence the development of their producers. In this context, measuring endogenous biogenic amine concentrations in the biomass and culture liquid of the two tested microalgae was of considerable interest.

***S. quadricauda* and *C. vulgaris* do not Synthesize Biogenic Amines and do Not Release them into the Culture Liquid**

High-performance liquid chromatography (HPLC) analysis failed to reveal any detectable amounts of serotonin, dopamine, norepinephrine, or DOPA (the dopamine precursor) in the samples of the culture liquid and the disintegrated biomass of *S. quadricauda* and *C. vulgaris* cultures taken during the stationary growth phase (day 7 and 4 of cultivation for *S. quadricauda* and *C. vulgaris*, respectively). These negative data are not presented in the form of a table in this work.

DISCUSSION AND CONCLUSIONS

Taken together, the data obtained indicate that all tested biogenic amines stimulate the growth of *S.*

quadricauda at relatively low (micromolar) concentrations. In a similar fashion, they are stimulatory to the culture of *C. vulgaris*, as follows from the data on norepinephrine presented in this work and the results for serotonin, dopamine, and histamine reported earlier in [1].

In the literature, there are data that another important neurochemical, acetylcholine, stimulates the growth of *Chlorella* species, e.g., *C. sorokiniana* [9]. Apart from accelerating the growth of *Chlorella*, this neurochemical brings about an increase in its total lipid content and the amount of unsaturated fatty acids such as α -linolenic acid, which is of practical interest in terms of using this alga to prepare drugs and biofuel [9].

Among the biogenic amines tested in this work, histamine proved to be the most powerful growth stimulator, and it produced an ~65% effect in *S. quadricauda* (this work) and an almost 100% effect in *C. vulgaris* [1]. Presumably, the mechanism of action of biogenic amines involves their binding to specific cell surface receptors, in analogy to other unicellular organisms [2]. Similar mechanisms operating in various representatives of microorganisms were postulated in the literature for catecholamines and other neuroactive biogenic amines [2, 10].

However, relatively high amine concentrations, such as 100 μ M, are less stimulatory to the growth of the algae than the lower tested concentrations. The assumption that high amine concentrations produce a nonspecific toxic effect (presumably associated with decoupling biological membranes [2]) might account for these data contained in the present work.

The findings concerning the stimulatory influence of micromolar amine concentrations seem to have potential biotechnological implications since such small amounts of the amines are relatively inexpensive. A project aimed at increasing the biomass yield of microalgae by adding histamine (or, plausibly, other neurochemicals) to their cultures holds some promise

with respect to promoting the production of drug preparations, food additives, or biofuel from microalgae.

In the literature, there is evidence that many algal species, including a number of representatives of *Chlorophyta*, *Charophyta*, *Ochrophyta*, and *Rhodophyta*, synthesize large quantities of such neuroactive amines as dopamine, serotonin, histamine, tyramine, and acetylcholine [11-12]. For instance, histamine accumulates up to concentrations of 60-500 mg/g of biomass in the red alga *Claviceps purpurea* [13].

However, in this work, the analysis of the content of disintegrated algal cells and the cultural liquid of *S. quadricauda* and *C. vulgaris* using HPLC revealed zero concentrations of serotonin, norepinephrine, dopamine, and the dopamine precursor DOPA in these microalgae.

Nevertheless, based on literature data, *Scenedesmus* species contain significant concentrations of other biogenic amines such as tyramine and ptomains [14], some of which may perform neurochemical functions [2].

The fact that the tested microalgae contain zero concentrations of endogenous serotonin, norepinephrine, and dopamine seems to rule out the suggestion that these neurochemicals can fulfill an autoregulatory function. Therefore, in the previous work [1], the hypothesis was put forward that biogenic amines and, presumably, other neuroactive compounds function as interspecies rather than intraspecies signals. The microalgal growth-promoting neurochemicals norepinephrine, dopamine, serotonin, and histamine are produced by other components of natural aqueous ecosystems in which microalgae form a part of the phytoplankton. Dopamine, norepinephrine, histamine, and serotonin are synthesized by various representatives of the microbiota [2], and, therefore, the impact of these compounds on microalgae can be considered in terms of chemical interaction between microalgae and other microorganisms. This interaction is apparently beneficial for microalgae with respect to their growth.

High dopamine concentrations are also released by such macroalgae as *Ulvaria*. In the literature, evidence has been presented that *Ulvaria*-produced dopamine functions as an antimicrobial agent and as a kairomone, i.e., a protective substance preventing the

consumption of *Ulvaria* by sea urchins, gastropods, and arthropods [13, 15, 16]. Presumably, the data reported in this work enable us to consider dopamine and plausibly other neurochemicals from a new perspective: these neuroactive substances are likely to function as growth-stimulating agents for microalgae in the natural ecosystems of ponds, lakes, and other water bodies.

Interestingly, not only *Ulvaria* but also other macroalgae, e.g., *Nitella flexilis* and *Chara vulgaris*, and also higher plants growing on the water surface such as the duckweed (*Lemna minor*) produce biogenic amines and release them into the environment [13, 17]

Submicromolar or micromolar concentrations of dopamine, norepinephrine, and serotonin are produced by a number of coastal plant species exemplified by tropical trees and shrubs growing around lakes and ponds in southern China (e.g., in Shenzhen [4]). Generally speaking, many higher plants both contain neurochemicals and respond to them [18, 19]. Biogenic amines produce strong stimulatory effects on the seeds of *Raphanus sativus*, the vegetative microspores of *Equisetum arvense*, and the pollen of *Hippeastrum hybridum* [19], in an analogy to the microalgae investigated in the present work.

Aqueous ecosystems typically contain invertebrates that also release neurochemicals (reviewed, [5]). Stress factors and traumas resulting from, e.g. predator attacks or interindividual fighting, increase the production of histamine, serotonin, and, frequently, catecholamines by aquatic animals. In light of the data presented in this work, these animal stress- or trauma-related products are expected to promote algal growth in natural water bodies. Overall, the tested biogenic amines appear to function as ecosystem-level communication signals termed in the literature as *ecomones* [20].

Apart from the ecological implications, the data obtained seem to hold some promise with respect to developing a relatively economical technique of boosting algal biomass production.

CONSENT FOR PUBLICATION

The authors confirm that all experiments with algae were performed in accordance with the national and international standards and guidelines. This article does not contain any studies involving animals performed by any of the authors.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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