

Growth Inhibition Underlies the Suppression of QseBC-Regulated Virulence by Trace Amines and Dopamine

(Perencatan Pertumbuhan Mendasari Penindasan Virulens yang Dikawal QseBC oleh Surih Amina dan Dopamin)

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ABSTRACT

Trace amines (TAs) and dopamine are neuroactive compounds that can interact with bacterial adrenergic receptors like QseC, a membrane-bound sensor histidine kinase. QseC is the core sensing component of the QseBC two-component system, which regulates virulence gene expression in Gram-negative pathogens via quorum sensing. This study investigated whether TAs (tryptamine, phenethylamine, tyramine) and dopamine act as specific QseBC modulators or exert indirect effects via growth inhibition in *Escherichia coli* O157:H7, *Salmonella Typhimurium*, and *Vibrio cholerae* O1. Our results show that at high concentrations (≥ 50 -250 $\mu\text{g/mL}$), these compounds significantly inhibited bacterial motility and modestly downregulated QseBC-regulated virulence genes (*ea*, *ler*, *sipA*, *sopB*) and Shiga toxin production. However, these effects were concurrent with a pronounced, concentration-dependent growth inhibition. While dopamine exhibited iron-chelating activity in the CAS assay, this did not mitigate its growth-suppressive effect. In conclusion, the anti-virulence effects of TAs and dopamine are secondary consequences of a general antibacterial activity that compromises cellular fitness, rather than a result of specific QseBC antagonism.

Keywords: Bacterial virulence; dopamine; growth inhibition; QseBC; trace amines

ABSTRAK

Surih amina (TA) dan dopamin adalah sebatian neuroaktif yang boleh berinteraksi dengan reseptor adrenergik bakteria seperti QseC, yang merupakan histidin kinase sensor yang terikat membran. QseC adalah komponen pengesanan teras sistem dua komponen QseBC yang mengawal selia pengekspresan gen virulens dalam patogen Gram-negatif melalui pengesanan kuorum. Penyelidikan ini mengkaji sama ada TA (triptamina, fenetilamina, tiramina) dan dopamin bertindak sebagai modulator QseBC khusus atau memberikan kesan tidak langsung melalui perencatan pertumbuhan dalam *Escherichia coli* O157:H7, *Salmonella Typhimurium*, dan *Vibrio cholerae* O1. Hasil menunjukkan bahawa pada kepekatan tinggi (≥ 50 -250 $\mu\text{g/mL}$), sebatian ini menghalang motiliti bakteria dengan ketara serta menurunkan pengekspresan gen virulens yang dikawal selia oleh QseBC (*ea*, *ler*, *sipA*, *sopB*) dan penghasilan toksin Shiga. Walau bagaimanapun, kesan ini serentak dengan perencatan pertumbuhan yang ketara dan bergantung kepada kepekatan. Walaupun dopamin menunjukkan aktiviti pengkelat zat besi dalam ujian CAS, ini tidak mengurangkan kesan penindasan pertumbuhannya. Kesimpulannya, kesan anti-virulens TA dan dopamin adalah akibat sekunder daripada aktiviti antibakteria umum yang menjejaskan kecergasan sel dan bukannya hasil daripada antagonisme QseBC tertentu.

Kata kunci: Dopamin; kevirulenan bakteria; perencatan pertumbuhan; QseBC; surih amina

INTRODUCTION

Chemical signalling between host and pathogen plays an important role in determining the outcomes of an infection (Munter & Frischknecht 2006; Olive & Sassetti 2016). Neurochemicals, one type of signal secreted by the host as well as other bacteria, such as catecholamines (epinephrine, norepinephrine, and dopamine) and trace amines (tryptamine, phenethylamine, and tyramine), are not only crucial in neuronal signalling but also in

modulating bacterial physiology (Luqman 2023; Luqman et al. 2020b; Lyte 2013). In Gram-negative pathogens, a key mediator for this interkingdom signalling is the QseBC system. The QseBC system is a quorum sensing system that recognizes epinephrine and norepinephrine as the activator beside AI₃, its indigenous autoinducer (Clarke et al. 2006; Hughes et al. 2009; Kim et al. 2020). Upon binding, epinephrine and norepinephrine stimulate a signalling cascade that upregulates the expression

of virulence factors, including flagella for motility and genes essential for infection or host cell invasion (Hughes et al. 2009; Moreira & Sperandio 2012; Moreira, Weinshenker & Sperandio 2010; Sperandio, Torres & Kaper 2002).

While it is established that epinephrine and norepinephrine are virulence-enhancing signals via QseC, the functional role of structurally related compounds like trace amines and dopamine in this pathway remains ambiguous and context-dependent. Furthermore, dopamine has been known to have siderophore-like properties, chelating iron to promote bacterial growth under iron-limited conditions (Dichtl et al. 2019; Perraud et al. 2022), which adds another layer of the complexity of their role in bacterial physiology.

This study aimed to investigate the effects of trace amines (tryptamine, phenethylamine, and tyramine) and dopamine on the QseBC system in three major Gram-negative enteropathogens: *Escherichia coli* O157:H7, *Salmonella enterica* serovar Typhimurium, and *Vibrio cholerae* O1. We evaluated their impact on QseBC-regulated phenotypes, such as motility, virulence gene expression, and toxin production, while simultaneously assessing bacterial growth and iron chelating capability.

MATERIALS AND METHODS

BACTERIAL CULTURE CONDITIONS

Three different bacterial strains were used in this study, namely *Escherichia coli* O157:H7, *Salmonella enterica* serovar Typhimurium, and *Vibrio cholerae* O1. All bacterial strains are obtained from the strain collection of the Microbial Genetics Department, University of Tuebingen. Bacteria were cultivated in basic medium (BM) (1% soy peptone, 0.5% yeast extract, 0.5% NaCl, 0.1% glucose and 0.1% K₂HPO₄, pH 7.2) and incubated at 37 °C with continuous shaking at 150 rpm for 24 h.

MOTILITY ASSAY

The motility of the bacterial strains was investigated using a motility assay that previously described (Croze et al. 2011; Luqman et al. 2021). Briefly, bacterial strains were inoculated in BM and incubated overnight at 37 °C with continuous shaking (150 rpm) and used as a pre-culture. The precultures were then re-inoculated into fresh BM medium and adjusted to get OD₆₀₀ of 0.1 and incubated for 4 h to reach mid-log phase and 3 µL of this bacterial culture was dropped on freshly prepared motility agar medium (1% tryptone, 0.5% yeast extract, 1% NaCl and 0.25% agar) containing different concentrations of trace amines and dopamine (50, 100,

250, and 500 µg/mL). The plates were then incubated at 37 °C for 24 h and the radius of the swarming area was measured by measuring the radius at 3 different positions and calculating the mean.

REAL-TIME POLYMERASE CHAIN REACTION (RT-PCR)

The expression of virulence-encoding genes in *E. coli* O157:H7 (*eae* and *ler*) and *S. Typhimurium* (*sipA* and *sopB*) with the *rpoB* gene as the housekeeping gene were determined using RT-PCR. These strains were inoculated in BM with supplementation of trace amine or dopamine at certain concentrations and incubated at 37 °C with continuous shaking at 150 rpm. The bacterial cells were harvested after 16 h incubation and the RNA was isolated using the Total RNA Purification Kit - Blood/Cell culture (Genaxxon, Germany) according to the protocol provided by the supplier. RT-PCR was carried out using Power SYBR™ Green RNA-to-CT™ 1-Step Kit (Thermo Fisher, USA). The thermal cycling conditions were a first holding at 48 °C for 30 min, a second holding of 95 °C for 10 min followed by 40 cycles of two steps: a first stage of 95 °C for 15 s and a second of 60 °C for 1 min. The primers used in this experiment are listed in Table 1.

SHIGA-TOXIN PRODUCTION

The production of Shiga toxin by *E. coli* O157:H7 was examined. *E. coli* was inoculated in BM and supplemented with trace amine or dopamine at certain concentrations: Tryptamine at 25, 50, 75, and 100 µg/mL while other trace amines and dopamine were at 100 µg/mL. The culture was incubated at 37 °C with continuous shaking at 150 rpm for 14 h. The supernatant was then collected and sterile filtered. StrataClean Resin was added to the supernatant to bind the proteins and incubated for 15 min under rotation at room temperature. The resin was collected by centrifugation, washed with PBS, and boiled with SDS sample buffer prior to running in 12% Tris-glycine gels (SERVA) (Ebner et al. 2017). Western blot analyses were then performed according to the previous publication by using anti-Shiga toxin purchased from Sino Biological to detect Shiga toxin in the samples (Ebner et al. 2015).

GROWTH CURVE

Bacterial strains from previously prepared precultures were inoculated in a fresh BM supplemented with tryptamine at the concentrations of 25, 50, and 100 µg/mL while other trace amines and dopamine at the concentration of 100 µg/mL. The culture was incubated at 37 °C with 150 rpm shaking. The OD₆₀₀ was measured at 0, 2 h, 4 h, 6 h, 8 h and 24 h.

TABLE 1. Primers used for RT-PCR

Primer	Sequence (5'-3')
rpoB <i>E. coli</i> F	ATCGAGCAAGATCCTGAAGGGC
rpoB <i>E. coli</i> R	GCGCTCATAGATCACCAGACGC
eae <i>E. coli</i> F	TCATGGTTGTTATACCCGGACC
eae <i>E. coli</i> R	AGATCGGCAACAGTTTCACCAG
ler <i>E. coli</i> F	GCGACTGCGAGAGCAGGAAG
ler <i>E. coli</i> R	ACGCCCAGCAGGTCTGC
rpoB <i>S. typ</i> F	ATCGAGCAAGATCCTGAAGGGC
rpoB <i>S. typ</i> R	TTTTACGCGCAGCGGTGC
sipA <i>S. typ</i> F	ATGCAGACCGAGATCAAAACGC
sipA <i>S. typ</i> R	CCGGCGACATTATTTGAATTGG
sopB <i>S. typ</i> F	ATGCAGATTCTCTCAGGCCAGG
sopB <i>S. typ</i> R	CCATTGACGTTAGAACCGGGTC

CHROME AZUROL S (CAS) ASSAY

The CAS assay was conducted according to the previous studies (Febrianti et al. 2025; Murakami et al. 2021; Schwyn & Neilands 1987). The CAS solution contains Chrome azurol S (0.15 mM) (Sigma), hexadecyltrimethylammonium bromide (0.6 mM) (Sigma), and FeCl₃ (1.25 mM) (Sigma). The iron-chelating activity of trace amines and dopamine was investigated by mixing the CAS solution with the compounds at a ratio of 1:1, and the absorbance was measured using a microplate reader at a wavelength of 630 nm. The decrease of the absorbance values represents the decrease of the CAS-Fe complex due to the Fe binding to the siderophore.

RESULTS AND DISCUSSION

The interaction between host-derived neurochemicals and bacterial receptors has been reported to be able to modulate the infection outcomes. However, some of these compounds also possess concentration-dependent antimicrobial properties (Luqman 2023). This study aimed to investigate whether trace amines and dopamine act primarily as modulators of the QseBC quorum sensing or if their impact on bacterial virulence is due to growth inhibition.

TRACE AMINES AND DOPAMINE INHIBIT MOTILITY OF GRAM-NEGATIVE BACTERIA

Previous studies showed that trace amines and dopamine can interact with human adrenergic receptors with different action depending on the subtypes (Luqman & Ohlsen 2024; Rahmdel, Luqman & Gotz 2025). As Gram-negative bacteria possess a bacterial adrenergic receptor known as the QseBC system (Clarke et al. 2006; Hughes et al. 2009), one of the quorum sensing systems

in Gram-negative bacteria, we wanted to investigate whether these compounds can also affect this quorum sensing system by monitoring the QseBC-regulated phenotypes, such as motility and virulence gene expression (Bearson et al. 2010; Halang et al. 2015; Sperandio, Torres & Kaper 2002).

The effect of trace amine and dopamine on the motility of Gram-negative bacteria was evaluated by supplementing these compounds in the motility agar at certain concentrations. Tryptamine at various concentrations (50, 100, 250, and 500 µg/mL) was selected based on prior reports that high concentrations of tryptamine decrease pyocyanin production in *Pseudomonas aeruginosa* (500 µg/mL) and prodigiosin production in *Serratia marcescens* (125 µg/mL) (Luqman et al. 2021). The experiments showed that tryptamine significantly inhibited motility of *E. coli* O157:H7 and *S. Typhimurium* only at high concentrations (250 µg/mL), while in *V. cholerae* O1, tryptamine showed an inhibition effect starting from 50 µg/mL.

The motility inhibition activity of other compounds at a concentration of 250 µg/mL was also determined. It showed different tendencies on different species. In *E. coli* O157:H7, all compounds showed significant inhibition effect. Similar tendency also shown in *V. cholerae* O1, except for tyramine, while in *S. Typhimurium* only tryptamine showed motility inhibition activity (Figure 1).

The motility assays exhibited that tryptamine seems to have a general motility inhibition activity across these three different bacterial strains, and a similar result was reported as well in *E. coli* K12 (Luqman et al. 2021). Moreover, another study also reported the potential of tryptamine in inhibiting biofilm in uropathogenic *E. coli* (UPEC) (Nair et al. 2024), suggesting that tryptamine might possess antivirulence properties. This suggests

that it is plausible that the exposure of relatively high concentrations of tryptamine, or trace amines in general, to bacteria affects its physiology (Otaru et al. 2024).

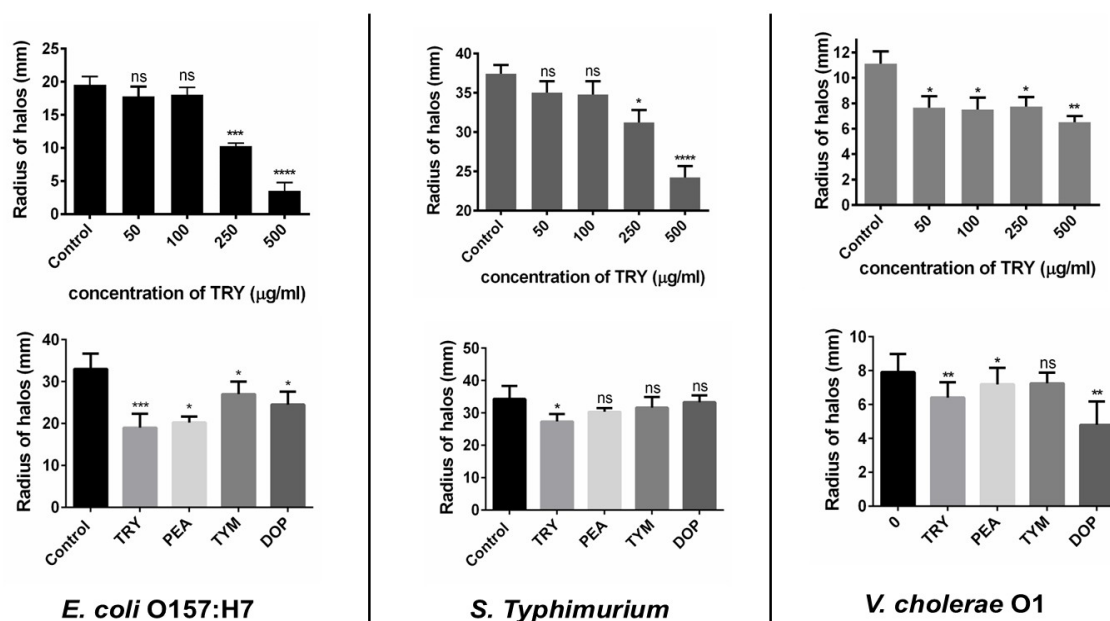
In contrast to its reported role as a motility enhancer in *V. harveyi* (Yang et al. 2014), our data identify dopamine as an inhibitor of motility in *V. cholerae*. The difference between these studies is that we used a higher concentration of dopamine, besides the difference in bacterial species. A study by Yang et al. (2014) showed that dopamine stimulates the motility of *V. harveyi* by acting as a QseC agonist, thus, increasing the expression of flagellar motility-related genes. This suggests that the effect of dopamine in *Vibrio* might be species- and concentration-dependent.

TRACE AMINES AND DOPAMINE DECREASED VIRULENCE GENES EXPRESSION IN GRAM-NEGATIVE BACTERIA AT HIGH CONCENTRATIONS

Besides the motility, we also investigated the effects of trace amines and dopamine on the expression of QseBC-regulated virulent genes, which are regulated by the QseBC system. The relative copies of the *eae* and *ler* genes in *E. coli* O157:H7 and *sipA* and *sopB* mRNAs in *S. Typhimurium* were monitored (Hughes et al. 2009; Moreira & Sperandio 2012; Moreira,

Weinshenker & Sperandio 2010). The gene expression in *V. cholerae* O1 was not determined because there is little known about the genes that are regulated by QseBC. For the gene expression analyses, various concentrations of trace amines and dopamine were added into the medium and cultivated the bacteria in those supplemented media. RNA in the late exponential phase, 16 h after inoculation, was isolated for expression analysis.

The result showed that 100 µg/mL of tryptamine significantly decreased the expression of *eae* and *ler* in *E. coli* as well as *sipA* and *sopB* in *S. Typhimurium*. The presence of other trace amines and dopamine (100 µg/mL) also decreased the expression of these virulent genes (Figure 2(A)). As Shiga toxin in *E. coli* is encoded by the *stx* operon and also regulated by the QseBC system (Hughes et al. 2009), the shiga toxin production of *E. coli* O157:H7 in the presence of trace amines and dopamine was also investigated. Western blot analysis was performed to detect shiga toxin in the supernatant of *E. coli* overnight cultures. First, the effect of tryptamine at various concentrations on shiga toxin production was tested, which resulted in a slight decrease at the presence of tryptamine at concentrations of 75 and 100 µg/mL. Then, other compound effects on shiga toxin production at the concentration of 100 µg/mL were also tested. The results showed that



For all graphs, each data point is the mean value $\pm$ SEM (n = 4); *p < 0.05; **p < 0.01; ***p < 0.001; and ****p < 0.0001, Student's t test was used for statistical calculations. TRY: tryptamine; PEA: phenethylamine; TYM: tyramine; DOP: dopamine

FIGURE 1. Trace amines and dopamine inhibit motility of Gram-negative bacteria at high concentrations.

Motility of *E. coli* O157:H7, *S. Typhimurium*, and *V. cholera* O1 was measured in the presence of tryptamine (TRY) at various concentrations with radius of halo represents the extent of the bacterial population spread on the agar. 250 µg/mL of TRY in the agar significantly inhibited the motility of *E. coli* and *S. Typhimurium* while the motility of *V. cholera* significantly inhibited in the presence of 50 µg/mL of TRY. Motility was also measured in the presence of various compounds (250 µg/mL). Trace amines and DOP (250 µg/mL) significantly inhibited the motility of *E. coli* and *V. cholera*, except TYM for *V. cholera* while the motility of *S. Typhimurium* only significantly inhibited in the presence of TRY

100 µg/mL of tryptamine, phenethylamine, and dopamine had a slight decreasing effect on Shiga toxin production (Figure 2(B)).

Our results indicate that trace amines and dopamine inhibit the expression of QseBC-regulated virulence genes, although the reduction was approximately only 0.1 unit (Figure 2) and only at high concentrations. This contrasts with findings from a different regulatory pathway, the EmrR-dependent pathogenicity island in *Salmonella* and *E. coli*, where dopamine was reported to stimulate gene expression (Yang et al. 2019). This contradiction can be explained by the distinct regulatory mechanisms involved; the inhibitory effect may be specific to the QseBC cascade, while the stimulatory effect reported elsewhere operates through an independent EmrR-dependent pathway.

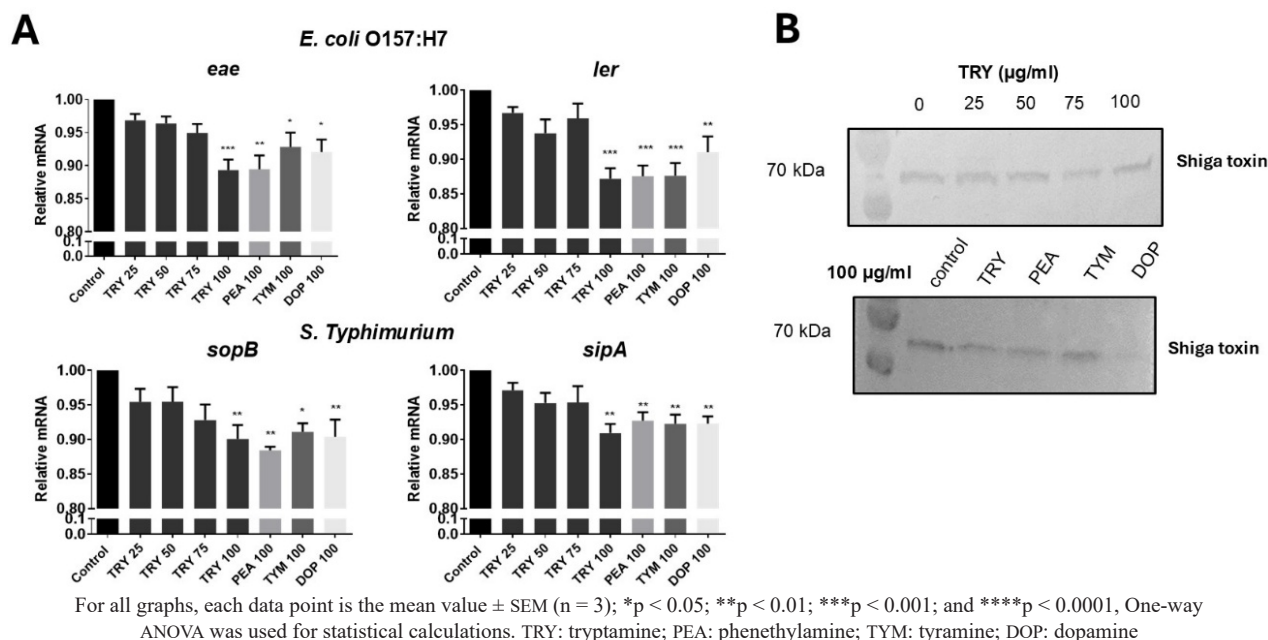
TRACE AMINES AND DOPAMINE INHIBIT THE GROWTH OF GRAM-NEGATIVE BACTERIA

The bacterial growth in the presence of trace amines and dopamine was monitored to confirm whether the decrease of QseBC-regulated phenotype expression was due to a growth inhibition or the ability of trace amines and dopamine to block the QseBC system. The decrease in growth of all Gram-negative bacteria in the presence

of trace amines was statistically significant. Even in the presence of a low concentration of tryptamine (25 µg/mL), it showed a significant decrease to the growth (Figure 3(A)).

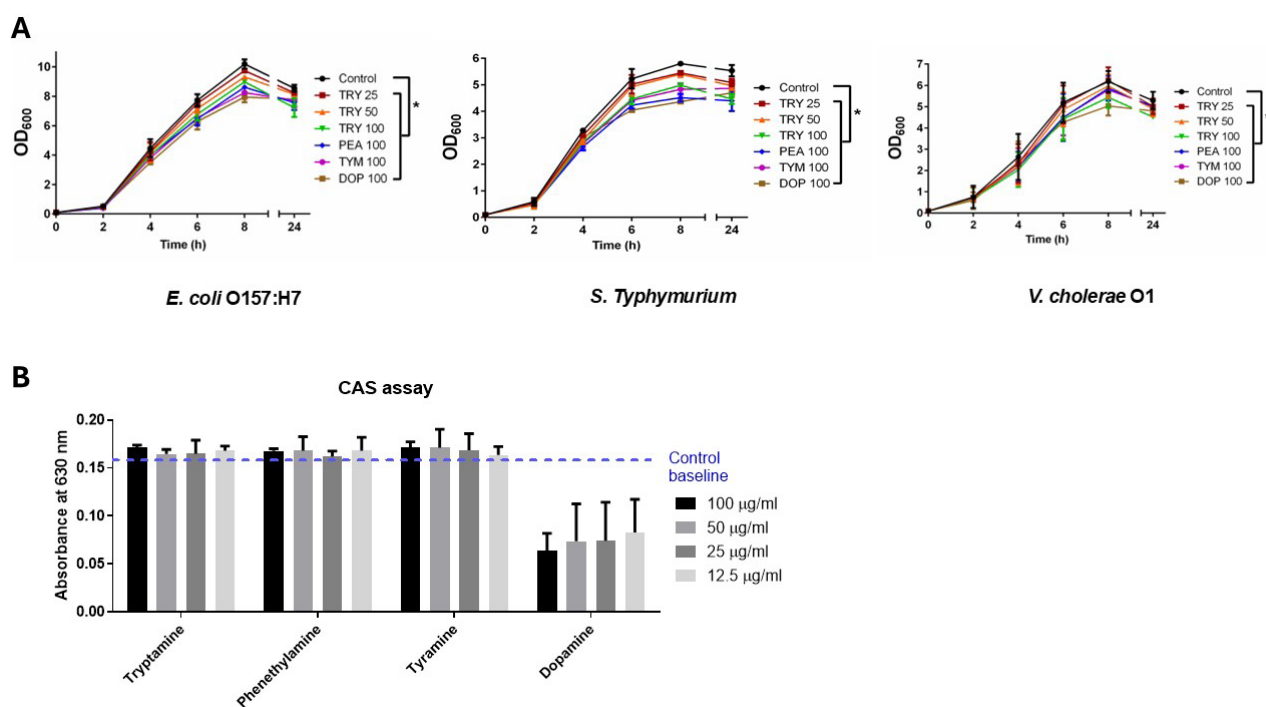
A similar tendency was also reported in *Serratia marcescens* and *Pseudomonas aeruginosa* in the presence of tryptamine (Luqman et al. 2021). This suggests that the suppression of QseBC-regulated phenotypes observed in this study is most probably to be the secondary consequence of the bacterial growth inhibition instead of the direct QseBC antagonistic effect. This is supported by a prior study that reported that trace amines and dopamine have no significant effect on QseC kinase activity *in vitro*, although the *in silico* study predicted that these compounds have similar binding affinity on QseC as epinephrine (Luqman et al. 2020a).

The siderophore activity of these compounds was also investigated. Trace amines showed no activity, but dopamine was tested positive (Figure 3(B)). Although dopamine's iron-chelating property is widely reported to promote bacterial growth (Dichtl et al. 2019; Febrianti et al. 2025; Perraud et al. 2022), our results showed the opposite effect. We propose that at the high concentration used in our study, dopamine's growth-inhibitory activity overwhelms the potential growth benefit from iron chelation.



For all graphs, each data point is the mean value $\pm$ SEM ($n = 3$); * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; and **** $p < 0.0001$, One-way ANOVA was used for statistical calculations. TRY: tryptamine; PEA: phenethylamine; TYM: tyramine; DOP: dopamine

FIGURE 2. Trace amines and dopamine inhibit the expression of the QseBC-regulated genes. (A) Trace amine and dopamine were added to the medium at certain concentrations. The expression of the genes was analysed using RT-PCR at 16 h after inoculation of *E. coli* O157:H7 and *S. Typhimurium*. (B) Shiga toxin production in the supernatant of *E. coli* O157:H7 was also monitored at 14 h after inoculation in the medium where TAs and DOP were added at certain concentration



For all graphs, each data point is the mean value $\pm$ SEM (n = 4); *p < 0.05, paired t-test was used for statistical calculations. TRY: tryptamine; PEA: phenethylamine; TYM: tyramine; DOP: dopamine

FIGURE 3. Growth curves of Gram-negative bacteria in the presence of trace amines and dopamine. (A) *E. coli* O157:H7, *S. Typhimurium*, and *V. cholera* O1 were inoculated in BM medium in the presence of trace amines and dopamine at various concentrations (25; 50; and 100 μ g/mL). The growth was monitored at OD₆₀₀ for 24 h. (B) Iron-chelating property of trace amines and dopamine were also tested using CAS assay and resulted only dopamine showed to be positive

CONCLUSIONS

In summary, our findings demonstrate that the motility inhibition and the decrease in virulent gene expression caused by trace amines and dopamine are secondary consequences of the growth inhibition activity, rather than a result of QseBC-specific antagonism. The observed growth inhibition indicates a compromised overall bacterial fitness due to exposure to high concentrations of these compounds.

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