
**Review**

The Monoamine Regulon Including Syntheses of Arylsulfatase and Monoamine Oxidase in Bacteria

Yoshikatsu MUROOKA,* Hiroyuki AZAKAMI,¹ and Mitsuo YAMASHITA

Department of Biotechnology, Graduate School of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka 565, Japan

Bacterial cells respond to monoamine compounds, such as tyramine, dopamine, octopamine, or norepinephrine, and induce the syntheses of tyramine oxidase encoded by *tyrA* and monoamine oxidase encoded by *maoA*. These monoamine compounds also derepress the synthesis of *atsA*-specific arylsulfatase that is repressed by sulfur compounds. These complex mechanisms of regulons regulated by monoamine and sulfur compounds have been analyzed by cloning and characterization of genes that are involved in the repression and derepression of the synthesis of arylsulfatase. The *atsA* gene forms an operon with the *atsB* gene, which encodes an activator of the expression of *atsA*. The negative regulator gene for arylsulfatase was found to code for dihydrofolate reductase (*folA*). The *maoA* gene forms an operon with the *maoC* gene, which has similarity to a dehydrogenase involved in the tyramine metabolism. The *maoF* gene encoding a 30-kDa protein, which is induced by tyramine, also forms an operon with the *maoE* gene. Finally, the *maoR* gene, which is induced by monoamine, was found to play a central role in the positive regulation of the expression of the monoamine regulon (*mao*) including the *atsBA*, *maoCA*, *maoEF*, and *tyr* operons. The *maoR* expression is subject to autogenous regulation and to cAMP-CRP control. The MoaR protein has a helix-turn-helix motif in its C terminus. Thus, the MoaR protein probably regulates the operons by binding to the regulatory region of the *mao* regulon.

**Key words:** sulfate regulon; monoamine regulon; arylsulfatase; monoamine oxidase; *Klebsiella*

The finding of the phenomenon of a red coloration of a newspaper in urine putrefied by bacteria has been developed to the study of synthesis of microbial arylsulfatase. This phenomenon was found by Harada about 45 years ago.¹ Arylsulfate esters are present in urine as compounds, such as phenyl sulfate and urineindican (indoxyl sulfate). Microorganisms growing in putrefying urine produced arylsulfatase to hydrolyze arylsulfate esters. When urineindican is hydrolyzed, inorganic sulfate and indoxyl are released. The indoxyl is converted to indirubin or indigo in the presence of oxygen (Fig. 1). When lignin and aldehyde radical are present indoxyl reacts with lignin to form a stable red substance.²³ Harada also found that production of arylsulfatase in bacteria varied greatly depending on the sample of polypeptone added to the culture medium.³¹ He finally purified the stimulation factor and identified the stimulator of arylsulfatase synthesis as tyramine.⁴¹ This is the first case of identification of a natural inducer for the synthesis of an enzyme. In addition to tyramine, octopamine, dopamine, and norepinephrine were also effective. Later, Okamura *et al.* found that these compounds, which are known as neurotransmitters, induced tyramine (monoamine) oxidase synthesis.⁵¹

It has been interesting that in the analysis of the relationship between the regulation of arylsulfatase synthesis and monoamine metabolism there seemed to be no similarity in the enzymes or metabolites. Most studies on the regulation of arylsulfatase biosynthesis have been done with *Klebsiella aerogenes* (synonym *Aerobacter aerogenes*, *Klebsiella pneumoniae*) because the enzyme is absent from or present at only very low levels in most strains of *Escherichia coli* or *Salmonella typhimurium* used in molecular genetics. Therefore, a genetic analysis system in *K. aerogenes* has to be developed in our laboratory.

**Repression of Arylsulfatase Synthesis**

The synthesis of arylsulfatase is repressed by sulfur compounds such as sulfate, sulfite, sulfitide, thiosulfate, and cysteine, but the enzyme is synthesized constitutively in cells grown with methionine or taurine as the sole source of sulfur.⁶,⁷ Mutant strains of *K. aerogenes* that were defective in the synthetic pathway from sulfate to cysteine were isolated.⁷ However, in these *atsC* mutants, the patterns of repression of arylsulfatase by sulfate or cysteine persisted like that of the wild-type strain. Arylsulfatase synthesis in the *atsC* mutant was not repressed by inorganic

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* Corresponding author.
¹ Present address: School of Dentistry, Tokushima University, Tokushima 770, Japan.

Fig. 1. Hydrolysis of Urineindican by Arylsulfatase and Reaction of Colorization.
sulfate but was repressed by cysteine. This mutant strain had a normal level of inorganic sulfate transport. Another mutant strain, defective in the inorganic sulfate transport system, synthesized arylsulfatase in the presence of inorganic sulfate but not of cysteine. These results suggest that there are two independent functional corepressors of arylsulfatase synthesis.

Arlsulfatase constitutive mutant strains were isolated. In these atsR mutants, the enzyme was synthesized constitutively regardless of the source of sulfur. These results suggested that the gene coding for arylsulfatase, atsA, was repressed by the atsR gene in the presence of sulfate or cysteine as the corepressor. The deprivation of these repressing sulfur sources in the medium did not significantly derepress arylsulfatase synthesis. This regulation pattern is quite different from that of alkaline phosphatase in E. coli, which is strongly derepressed by withdrawal of inorganic phosphate. The atsR mutations were more than 90% cotransducible with atsA mutations by PWS2 bacteriophage transduction. However, no cis-trans test has demonstrated the relationship of the atsR gene to the atsA gene.

In other species of bacteria, Pseudomonas putida and Staphylococcus aureus, arylsulfatases were produced when the cells were grown with methionine or one of the organosulfates or organosulfonamides as the sole source of sulfur. Under the same conditions, 7 to 14 proteins were newly synthesized by comparison with the conditions with inorganic sulfate or cysteine in these bacteria and E. coli.

Properties of Arylsulfatase
Arlsulfatase (EC 3.1.6.1) occurs in most animal tissues and in many microorganisms including fungi and Gram-positive and -negative bacteria. Its widespread distribution suggests that it may have a rather fundamental function. Since sulfates occur as organic sulfate, such as arylsulfate, in soil, arylsulfatase expression enables bacteria to use efficiently an alternative sulfur source during sulfur limitation. Arylsulfatase has thus become a model enzyme for studies on sulfate-regulated gene expression. Multiple forms of the enzyme are present in Salmonella, Proteus, Pseudomonas, and Mycobacterium species, and in many higher eukaryotes. In bacteria, the enzyme is usually in the periplasm or the cell membrane, though in fungi several intracellular forms are also known, usually associated with lysosome-like particles.

Arylsulfatases from K. aerogenes W70 cells grown in methionine medium (constitutive AtsA) and inorganic sulfate medium containing tyramine (derepressed AtsA) were purified and characterized. The two enzymes showed the same properties. The K_m and V_max were increased by addition of electron-withdrawing substituents. The enzymes were inhibited by inorganic phosphate, cyanide, hydroxylamine, and tyramine. The inhibition by tyramine was competitive (K_i = 1.0 × 10^{-4} M). These results show that the two enzymes were identical. This was also confirmed by the fact that atsA strains in which each have a single mutation site did not synthesize arylsulfatase under any conditions.

The enzyme from Serratia marcescens differed in K_m and V_max, substrate specificities, fluoride inhibition, and electrophoretic mobility from the K. aerogenes enzyme, but had the same molecular weight. The molecular weights reported range from 40,700 in Enterobacter aerogenes to 60,000 in P. aeruginosa. The optimum pH for the enzyme varies from 7.1 to 8.9 among different bacterial species.

For the purification of arylsulfatase from K. aerogenes, a simple, convenient method has been developed. This specificity of purification was done by using affinity chromatography on a tyrosine-hexamethylenediamino-β-1,3-glucan or on a solid phase immunoadsorbent. Antibody directed against the purified arylsulfatase from K. aerogenes W70 was obtained from rabbits. On the basis of the immunological properties of arylsulfatase, the strains in the family Enterobacteriaceae could be divided into two groups. Antisera formed a precipitin band with both active and inactive enzyme proteins from Escherichia, Citrobacter, Salmonella, Klebsiella, and Enterobacter, but not with the proteins from Serratia, Proteus, and Erwinia, even though some strains of these species had enzyme activity.

Development of Genetic Exchange Systems in K. aerogenes and Other Gram-negative Bacteria
Early work on the synthesis of arylsulfatase and used Aerobacter (Klebsiella) aerogenes ATCC9621. Since MacPhie et al. found a transducing phage PWS2 in K. aerogenes W70, further studies used this strain, including genetic analysis of mutant strains concerned with arylsulfatase synthesis. Systems for moving genes from K. aerogenes to E. coli and from E. coli to K. aerogenes or S. typhimurium by using P1 phage and the F episome were also developed. Murooka et al. extended the bacterial host range of P1 by using the heat-inducible phage P1Cr100KM, making it possible to transfer genes from E. coli to members of the family Enterobacteriaceae and some other genera of Gram-negative bacteria. However, the arylsulfatase gene, atsA_A, from K. aerogenes could not be transferred to E. coli, because the DNA sequence similarity of the atsA genes of these two bacteria is low. Dissimilar gene transfer between different bacteria would be possible with a Mu prophage of a transmissible plasmid and of the chromosome in a bacterial strain because of recombination between the two prophages. Thus, the bacterial host range of Mu was expanded and the conditions necessary for transfer of several genes, including ats_A, between taxonomically different bacteria by using RP4::Mucts were examined. During the course of these studies, Murooka et al. developed a general in vivo cloning method and cloned the ats-tyn region and the pullulanase gene, pulA, from K. aerogenes into E. coli.

Depression of Arylsulfatase Synthesis by Monoamine Compounds
The repression of arylsulfatase synthesis caused by the sulfur compounds is relieved by the addition of tyramine, octopamine, dopamine, or norepinephrine. These monoamine compounds induced tyramine oxidase synthesis by tynA in K. aerogenes. The derepression of arylsulfatase synthesis and the synthesis of tyramine oxidase occurred coordinately. The atsA and tynA genes were mapped on the chromosome of K. aerogenes by using F episomes from E. coli and the transducing phage P1. These genes
are linked to *gdhD* and *trp* in the order *atsR-atsA-tynA-gdhD-trp*.31

On the basis of classical genetic analysis, Murooka *et al.*80 proposed scheme of the regulatory mechanisms as shown in Fig. 2. In this model, arylsulfate ester is hydrolyzed to an aryl compound and inorganic sulfate by arylsulfatase encoded by *atsA*. The inactive repressor encoded by *atsR* is activated by a corepressor, which comes from inorganic sulfate and cysteine and could be governed by *atsS* and *atsC*, respectively. On the other hand, tyramine oxidase is specified by *tynA* and induced by specific monoamine compounds, such as tyramine or dopamine, which could be one of the products of the action of arylsulfatase on arylsulfate ester. Monoamine compounds are oxidized to hydroxyphenylethylamine compounds and ammonium ions. The synthesis of tyramine oxidase is subject to catabolite repression and ammonium repression and also repressed by *tynR*. The ammonium effect is independent of the function of cyclic AMP. It was thought that expression of the *tynA* gene resulted in derepression of arylsulfatase synthesis. Open and closed arrows represent positive and negative controls, respectively. Percent represents the cotransduction frequency by phage PW52.

Cloning and Characterization of *ats* Operon

As a step towards understanding the organization of genes in the *ats-tyn* region (Fig. 2), the genes involved in the synthesis of arylsulfatase from *K. aerogenes* were cloned into *E. coli*.33 In *E. coli* cells that carried the plasmid containing the *atsA*, the synthesis of arylsulfatase was

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Fig. 2. Model for the Regulation of Arylsulfatase and Tyramine Oxidase Syntheses.

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Fig. 3. The *ats* Operon in *K. aerogenes* (A) and the *mao* Operons in *K. aerogenes* and *E. coli* (B). In *K. aerogenes*, two monoamine oxidase genes (*tynA* and *maoA*) exist. The *maoA* gene forms an operon with *maoC* which encodes a CHMS dehydrogenase-like protein, and the operon is induced by monoamine compounds and controlled by cAMP-CRP. The *tynA* gene is induced by tyramine and subject to catabolite repression. In *E. coli*, the *maoA* gene is induced by monoamine compounds and positively regulated by the *maoB* gene which is subject to catabolite repression.
repressed by various sources of sulfur including methionine and taurine. Methionine and taurine caused to repression of the enzyme synthesis in *K. aerogenes* but strongly repressed it in *S. typhimurium* and *S. marcescens*. These organism-specific differences in the degree of the repression may be due to differences in the metabolic conversion of methionine or taurine into the actual corepressor for the *atsR* gene. The repression was relieved, in each case, by tyramine. The *atsA* gene complemented *atsA* mutation. The *atsR* acts in trans upon the *atsA* gene.

The *ats* operon is composed of two cistrons, the structural gene for arylsulfatase, *atsA*, and *atsB* (Fig. 3A). The operon is regulated at the transcriptional level by sulfur and tyramine. Deletion analysis and a lacZ fusion experiment suggested that *atsB* is a potential positive factor for arylsulfatase (Yamashita et al. unpublished results). Amino acid sequences of arylsulfatases from several sources, human sterol sulfatase, human arylsulfatase A, and sea urchin show two distinct regions with high sequence similarity.

Identification of the Negative Regulator Gene for Arylsulfatase Synthesis as *folA*

To analyze the molecular mechanism of the repression of the *atsA* gene by sulfur-containing compounds, the negative regulator gene from *K. aerogenes* was cloned by complementation of constitutive *atsR* mutations. The resultant gene was highly similar to the gene which codes for dihydrofolate reductase (*folA*) in *E. coli* and showed high enzyme activity. Transfer of a plasmid containing the *E. coli folA* gene into *atsR* mutant cells of *K. aerogenes* resulted in repression of the arylsulfatase synthesis. Thus, the *folA* gene encodes a negative regulator for the *ats* operon. Transduction experiments, however, showed previously that *atsR* is more than 90% linked with the *atsA* gene. While the *folA* gene is at 1 min on the *E. coli* chromosome, far from the location of the *E. coli* *atsA*-*atsB* homologs (85 min). Furthermore, the repressed levels by the multigene *folA* gene were not as low as that of the wild-type strain W70 with sulfate or cysteine. These results indicate that the product of the *folA* gene is different from the predicted *atsR* repressor. Recently, the previously isolated *atsR* mutants were confirmed to be 0° type mutations by sequence analysis (Azakami et al. unpublished result). Dihydrofolate reductase, which is a key enzyme in folic acid metabolism, may involve direct effects on *atsA* expression or metabolic effects on enzyme activity. In any case, the finding of *folA* as a negative regulator implies the existence of an unexpected regulatory connection between methyl (C8) metabolism and sulfur metabolism.

Monoamine-regulated Operons in *K. aerogenes* and *E. coli*

The *K. aerogenes* gene involved in the synthesis of monoamine oxidase was cloned and sequenced. Two open reading frames, the monoamine oxidase structural gene, *maoA*, and an unknown gene, *maoC*, were found (Fig. 3B). The deduced amino acid sequence of *maoC* has a significant similarity to 5-carboxymethyl-2-hydroxyxuanonate semi-aldehyde (CHMS) dehydrogenase of *E. coli* (Azakami et al., unpublished result). The CHMS is the product from tyramine by catalysis of monoamine oxidase. A region of the *E. coli* chromosome that was highly similar to the *Klebsiella maoA* gene was found. The potential *maoA* gene is at 30.9 min on the *E. coli* chromosome. Primer extension and SI nuclease mapping of transcripts generated in vivo suggest that the tyramine-induced mRNA starts upstream from the *maoC* gene. In the putative promoter region, a high degree of similarity to the consensus sequence for the binding site of cyslic AMP receptor protein was found. Thus, the *mao* region is composed of two cistrons, and the *mao* operon is regulated by monoamine compounds, glucose, and ammonium ions. We thought that this *maoA* gene was identical to the *tyrA* gene, which is involved in the derepressed synthesis of arylsulfatase, since the *maoA* gene complements the *tyrA* mutation. Recently, it was shown that *K. aerogenes* has two monoamine oxidase genes (*maoA* and *tyrA*) as discussed later.

A fragment containing the monoamine oxidase gene from the *E. coli* Kohara bank was subcloned. It seemed that two amine oxidase genes (*maoA* and *maoX*) were in the fragment. The nucleotide and amino acid sequences of one of the two genes are highly similar to those of the *maoA* gene and monoamine oxidase from *K. aerogenes*, respectively (Fig. 3B). These results and analysis of the enzyme activity showed that the gene codes for monoamine oxidase (*maoA*). The tyrosyl residue, which could be converted to topa quinone in the *E. coli* enzyme, was located by comparison with the amino acid sequence at the cofactor sites in other copper-topa quinone-containing amine oxidases.

The unknown gene (*maoX*), which was thought to be an amine oxidase adjacent to the *maoA* gene in *E. coli*, was ascertained not to be any amine oxidase but a positive regulator of the *mao* gene [Yamashita et al., *J. Bacteriol.*, 178, No. 10, (1996)]. Thus, the *maoX* gene was renamed *maoB*. The consensus sequence of the CAMP-CRP-binding domain was adjacent to the putative promoter of the *maoB* gene. By using lacZ fusions with *maoA* and *maoB* genes, we showed that the *maoA* gene is regulated by tyramine and Mabo protein and that expression of the *maoB* gene is subject to catabolite repression. Thus, it seems likely that monoamine and the Mabo protein activate the transcription of *maoA* by binding to the regulatory region of the *maoA* gene.

Properties of Monoamine Oxidases from *K. aerogenes* and *E. coli*

Monoamine oxidases are distributed widely in Gram-negative and -positive bacteria in addition to a variety of eukaryotes. Tyramine oxidase from *K. aerogenes* could not be characterized, since the enzyme bound tightly to the cell membrane and failed to solubilize in an active form. Cloning of the gene for tyramine oxidase from *K. aerogenes* resulted in overproduction of the enzyme in a soluble form, thus making its purification and characterization possible. The enzyme has a molecular weight of about 79,000, which is identical to that deduced from the nucleotide sequence of the *maoA* gene. The enzyme catalyzed the deamination of β-phenethylamine, dopamine, tryptamine, and octopamine, but not diamines, polyamines, or amino acids. The enzyme did not have a typical flavoprotein spectrum, but the enzymatic activity increased linearly with increasing amounts of added copper. The purified enzyme was found to contain copper.
Cooper et al.\(^{40}\) reported that the amine oxide from *E. coli* K-12 grown on 2-phenethylamine contains copper and topa quinone as cofactors. The translated amino acid sequence of the *E. coli* maoA gene included the consensus sequence of topa quinone, Asn-Tyr-Asp-Tyr. A comparison of the amino acid sequence of amine oxidases from yeast,\(^ {41}\) *E. coli*,\(^ {52}\) and *K. aerogenes* W70\(^ {51}\) suggests the enzyme strain W70 could be a copper- and topa quinone-containing monoamine oxidase. From these results, we classified the enzyme obtained from *K. aerogenes* W70 in the soluble form as a monoamine oxidase (EC 1.4.3.6) instead of a tyramine oxidase (EC 1.4.3.9), and hence the gene encoding this enzyme was renamed from *tyrA* to *maoA*. By the gene targeting method, the *maoA*C operon in *K. aerogenes* W70 was disrupted.\(^ {48}\) Since the *maoA* mutated strain still has monoamine oxidase activity and the previously isolated *tyrA63* mutant strain has no activity of monoamine oxidase, the *maoA* gene on the W70 chromosome is probably silent and the *tyrA*-specified tyramine oxidase is active in *K. aerogenes* W70.

Roh et al.\(^ {49}\) characterized monoamine oxidase from *E. coli*. The enzyme was overproduced by subcloning of the *maoA* gene in the periplasmic space. The enzyme was found to be a dimer of identical subunits with a molecular weight of 80,000, while *K. aerogenes* MaoA is a monomer with a *M*\(_{s}\) of 79,000.\(^ {45}\) The *E. coli* enzyme oxidized tyramine, phenethylamine, and tryptamine at higher rates, but not oxidized diamin and polyamines. The antibody against *E. coli* MaoA cross-reacted with purified MaoA from *K. aerogenes*. This copper-topa quinone-containing MaoA from *E. coli* has been crystallized. The crystals diffract X-rays to a resolution limit of at least 2.7Å and are resistant to X-ray radiation damage.\(^ {50}\) These crystals appear to be suitable for X-ray structure analysis. The biogenesis of topa quinone and tryptophan tryptophylquinone coenzymes was reviewed by Tanizawa.\(^ {51}\)

**moaR, A Gene That Encodes a Positive Regulator of the Monoamine Regulon**

To study the mechanism of the coordinated expression of proteins induced by monoamine compounds, a gene involved in the derepression of the synthesis of arylsulfatase was cloned and characterized.\(^ {52}\) The gene was cloned by complementation of a *K. aerogenes* mutant, K801, in which tyramine fails to relieve the arylsulfatase repression caused by sulfur compounds (Fig. 4). This *moaR* gene plays a central role in the positive regulation of the expression of the monoamine regulon including the *atsBA* and *tyrA* operon. The *moaR* gene on the chromosome of the wild-type strain of *K. aerogenes* was disrupted by the gene disruption method with a plasmid containing the inactivated *moaR*. The resultant mutant showed the same phenotype as previously isolated *atsT* mutant strains\(^ {59}\) that exist no more, but are negative for the derepressed synthesis of arylsulfatase (Fig. 4). In this mutant strain, tyramine also failed to induce the synthesis of tyramine oxidase.\(^ {52}\)

The *moaR* gene is capable of encoding a protein of 26,238 Da. The amino acid sequence is similar between the C-terminal domain of MoaR and the conserved sequences in the C-terminal regions of members of the UhpA subfamily (FixJ, ComA, and NarL, etc.) of response regulators with two-component systems.\(^ {53}\) However, in the MoaR sequence, no conserved sequence for phosphotransfer in the N-terminal region was found. The putative MoaR protein has a helix-turn-helix motif in its C terminus. Thus, it seems likely that the MoaR protein regulates the ope- rons by binding to the regulatory region of the monoamine regulon. The MoaR protein is subject to autogenous control, which was shown by use of a *moaR*-lacZ transcriptional fusion. The *moaR* gene is also subject to catabal- lote repression, and the repression is overcome by cAMP [Yamashita et al., *J. Bacteriol.*, 178, No. 10, (1996)].

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<tr>
<th>Strain</th>
<th>Growth with tyramine</th>
<th>AtsT derepression</th>
<th>MaoA synthesis</th>
<th>30kDa protein synthesis</th>
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**Fig. 4.** Characteristics of the Mutant K801 and the *moaR* Gene. Strain K801 was isolated as a mutant which failed to derepress arylsulfatase synthesis by tyramine: pAT11 contains the *moaR* gene.

The *moaEF* Operon Is Controlled by the Positive MoaR Regulator

A 30-kDa protein accumulated upon induction by a high concentration of tyramine or dopamine in cells of *K. aerogenes* was also cloned.\(^ {54}\) These cells carried a plasmid that included the *atsBA* operon. Two ORFs, *moaE* and *moaF*, are located downstream of the *atsBA* operon.\(^ {54}\) Transcription from a putative promoter of *moaE* was induced by the addition of tyramine, and the *moaF* gene was co-transcribed from this monoamine-inducible promoter. The deduced MoaE protein was similar to insect-type alcohol dehydrogenase. The amino acid sequence from the N-terminus of the purified 30-kDa protein agreed with that deduced from the nucleotide sequence of *moaF*. Using a *Klebsiella aerogenes* strain with a mutant *moaR* gene, we found that the gene (*moaR*) that acts as a positive regulator of the monoamine regulon also acts as the positive regulator of the *moaEF* operon. The discovery of this new operon regulated by MoaR may be an indication of a more interesting role for the monoamine regulon in living cells.

On the basis of these new findings, a schematic model of the MoaR regulated monoamine regulon was re-proposed (Fig. 5). The expression of the *moaR* gene is subject to catabolite repression and also induced by monoamines, such as tyramine, octopamine, dopamine, and norepinephrine, via a predicted sensor and signal transduction, but may not be simply induced by monoamines to bind to the activator. The expression of *moaR* is induced by MoaR and the over-production of MoaR results in the repression of MoaR synthesis. The MoaR protein induces the *atsBA* operon containing the structural gene for arylsulfatase (*atsA*) which is repressed by sulfur compounds *via* a negative

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Fig. 5. Schematic Model of the MoaR-regulated Monoamine Regulon.

For explanation of this model, see text. The following genes are encoding proteins: *apoH*, diadenosine tetraphosphate; *atxA*, arylsulfatase; *atxR*, positive regulator for arylsulfatase; *folA*, dihydrofolate reductase; *moaC*, monoamine oxidase; *moaF*, CHMS dehydrogenase-like protein; *moaL*, 30kDa protein induced by tyramine; *moaR*, positive regulator for monoamine regulon; *tynA*, tyramine oxidase. Symbols: P, promoter; open arrow, positive control; closed arrows, negative control; horizontal open arrows, direction of ORFs.

regulator, FolA. MoaR also positively regulates the *tynA*, *moaCA*, and *moaEF* operons by most probably binding to their promoter region of DNA.

The study on the mechanism of arylsulfatase synthesis resulted in discovering of the monoamine regulon. The intersection crossing across the sulfate regulon and the monoamine regulon may be more complicated. The metabolic pathways of C1-compounds and pathways regulated by nitrogen and stringent control may also cross over this intersection. Both enzymes, arylsulfatase and monoamine oxidase, which are induced by neurotransmitters, such as dopamine, octopamine, or norepinephrine, are not essential any more to growth of bacterial cells. On the other hand, arylsulfatase and monoamine oxidase exist in brain cells and are important in the human nervous system. These facts may suggest that the network systems studied here in enteric bacteria may have evolved to work in human brain cells.

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