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Control of Utilization of L-Arginine, L-Ornithine, Agmatine, and Putrescine as Nitrogen Sources in *Escherichia coli* K-12

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The regulation of the synthesis of the enzymes involved in the utilization of L-arginine, L-ornithine, agmatine, and putrescine as a sole nitrogen source in *Escherichia coli* K-12 was examined. The synthesis of agmatine ureohydrolase, putrescine aminotransferase, and pyrroline dehydrogenase is dually controlled by catabolite repression and nitrogen availability. Catabolite repression of agmatine ureohydrolase, but not that of putrescine aminotransferase or pyrroline dehydrogenase, is relieved by the addition of cAMP. Agmatine ureohydrolase synthesis in addition is subject to induction by L-arginine and agmatine. Arginine decarboxylase and ornithine decarboxylase synthesis is not sensitive to catabolite repression or to stimulation by nitrogen limitation or subject to substrate induction.

Nitrogenous compounds such as arginine, ornithine, and putrescine can be utilized by bacterial cells as both a carbon and a nitrogen source. The question of how the cell effectively regulates the utilization of such a carbon source without limiting its supply of nitrogen is of considerable importance and interest. The utilization of carbon sources is widely controlled by catabolite repression (13). In catabolite repression-sensitive systems, enzyme synthesis is repressed in a glucose minimal medium and derepressed on growth on a leaner carbon source such as succinate. In the catabolism of a compound that can provide both the carbon and nitrogen requirements of the cell, a simple exercise of this form of control could lead to a suicide situation as has been described by Neidhardt and Magasanik for *Salmonella typhimurium* (20). When grown in a glucose-histidine medium, *Salmonella typhimurium* is unable to utilize the nitrogen of histidine because of catabolite repression of the histidine utilization (*hut*) enzymes. In *Klebsiella* sp. and *Escherichia coli*, catabolite repression of the synthesis of enzymes catalyzing the utilization of nitrogenous carbon compounds is modulated by the state of nitrogen supply. When nitrogen is limiting the catabolite repression of these enzymes by glucose is overridden. The role of *gln* regulatory elements in this dual-control arrangement has been established both in *Klebsiella* sp. (14, 22, 25) and in *E. coli* (14, 28).

In this study we examine the effects of catabolite repression and nitrogen limitation on the synthesis of the enzymes which catalyze the utilization of arginine, ornithine, and putrescine as a source of nitrogen in *E. coli* K-12. The effects of cAMP and mutations at the *cya* and *crp* loci specifying the synthesis of adenylate cyclase and CAP protein, respectively, and of *gln* mutations affecting the regulation of nitrogen metabolism on enzyme synthesis in the arginine-ornithine degradative pathway are also described.

MATERIALS AND METHODS

Bacterial strains. *E. coli* K-12 strains used in this study are listed in Table 1.

Growth media, cultivation of bacteria, and genetic procedures. Media, cultivation methods, and genetic procedures have been described in the accompanying report (24).

Extract preparation and enzyme assays. Extracts were prepared and checked for enzyme activities as described in the accompanying report (24).

Introduction of *crp* gene. The enhancement effect of cAMP on streptomycin lethality described by Artman and Werthamer (1) was exploited to introduce the *crp* gene into CS101B and CS101By83 (*cya*). The two strains were grown in glycerol-ammonia minimal medium to mid-log phase (6×10^8 cells per ml). The cells were irradiated with UV light (120 s, 25 cm; Mineral Light; UV Light Products, San Gabriel, Calif.), diluted 1:1 in minimal medium, and allowd to double. A 0.1-ml fraction of a 1:10 dilution of each culture was plated onto glucose-ammonia minimal medium with 2.5 μg of streptomycin per ml (a sublethal dose for Str^s cells). In the center of the plate we spotted 50 μl of a 50 mM solution of cAMP, and the plates were incubated at 37°C. After 2 days there appeared a zone of inhibition in the center of the plate, and within this zone there appeared single colonies. These colonies were tentative *crp* mutants as they were not affected by the enhancement of streptomycin lethality by cAMP, presumably because they were unable to bind cAMP due to a lack of CAP protein (*crp*). These single colonies were picked and checked for growth on rhamnose, arabinose, galactose, and lactose with and without the addition of 10 mM cAMP. One colony of each strain that did not respond to cAMP and remained lactose-, rhamnose-, arabinose-, and galactose-negative was isolated, and the levels of β-galactosidase formed in glucose-ammonia medium with and without the addition of cAMP were measured. These Crp^- strains exhibited low levels of β-galactosidase and did not respond to cAMP (strains CS101B Crp^- and CS101By83 Crp^-).

RESULTS

Relationship to the *gab* regulatory system. The synthesis of the arginine, ornithine, and putrescine degradative enzymes is not affected by a mutation at the *gabC* locus that causes a severalfold increase in the rate of synthesis of the γ-aminobutyric acid (GABA) degradation enzymes (Table 2). The growth rates of the *gabC* mutant CS101B on arginine, ornithine, and putrescine do not differ from those observed with the wild-type parent CS101A. However, a *gab* mutation

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TABLE 1. *Escherichia coli* K-12 strains used

Strain	Relevant genotype or phenotype	Source or reference
CS101A	*metB*	17
CS101B	*metB gabC*	17
M-20	*metB gabC gabT*	17
AT713	*argA21*	B. Bachmann
CS101B713	*metB gabC argA21*	Transduction: AT713 → CS101B
CS101B Prr⁻	Pyrrolidine nonutilizing	24
CS101By83	Cya⁻	UV-induced mutation of CS101B
CS101B Crp⁻	Crp⁻	UV-induced mutation of CS101B
CS101By83 Crp⁻	Cya⁻ Crp⁻	UV-induced mutation of CS101By83
CS101BG	Gln⁻	28
CSA101BC	GlnC	28

that causes a several-fold decrease in the activity of GABA aminotransferase (GSST) and results in the inability of mutant strain M-20 to grow on GABA as the source of nitrogen, also reduces the activity of putrescine aminotransferase (PAT) and pyrroline dehydrogenase (Table 2) but does not significantly affect the mutant's growth on arginine, agmatine, ornithine, and putrescine.

Induction. In *Klebsiella aerogenes* the synthesis of enzymes catalyzing the degradation of nitrogenous compounds such as arginine or agmatine is inducible (7, 8). In contrast, the GABA degradative pathway in *E. coli* K-12 is not an inducible system (17). Since the degradation of arginine, ornithine, and putrescine in *E. coli* leads to the formation of GABA, it was of interest to see whether this pathway is controlled by induction. To avoid the problem of the endogenous pool of arginine, the *argA21* lesion of strain AT713 that blocks synthesis of arginine was introduced by transduction into CS101B. The induction experiments were carried out with this arginine-requiring derivative of CS101B (CS101B713). Addition of L-arginine, agmatine, and L-ornithine to cultures growing in a glucose-glutamine medium at 30°C (condition of nitrogen limitation) did not enhance L-arginine decarboxylase (ADC) or L-ornithine decarboxylase (ODC) synthesis (Table 3). However, addition of L-arginine or agmatine but not L-ornithine, putrescine, or GABA, resulted in a three- to fourfold higher rate of agmatine ureohydrolase (AUH) synthesis. The synthesis of PAT was only slightly enhanced in the presence of L-arginine, agmatine, L-ornithine, and putrescine in the medium.

TABLE 2. Enzyme activities in strain CS101A, in its *gabC* mutant CS101B, and in the GABA-nonutilizing mutant M-20[a]

Strain	Sp act (nmol/min per mg protein) of the following enzymes:						
	ADC	AUH	ODC	PAT	PrrD	GSST	SSDH
CS101A	185	220	170	17	960	25	17
CS101B	195	190	162	17	975	380	850
M-20	200	190	210	5	150	80	675

[a] Cells were grown in succinate-ammonia minimal medium as described in the text.

TABLE 3. Effect of inducers on enzyme synthesis in strain CS101B713[a]

Inducers added	Enzyme activity (nmol/min per mg protein)					
	ADC	ODC	AUH	PAT	GSST	SSDH
None	178	190	152	26	1,276	1,206
L-Arginine	220	184	500	44	957	1,306
Agmatine	187	198	475	44	784	919
L-Ornithine	200	192	170	46	995	1,572
Putrescine	208	208	190	56	1,162	1,832
GABA	213	195	194	34	670	670

[a] Strain CS101B713, an arginine-requiring derivative of CS101B unable to synthesize ornithine, was used to limit internal pools of ornithine and arginine. Cells were grown at 30°C with glucose (0.5%) as the carbon source and glutamine (0.01%) as the source of nitrogen. The inducers were added to a final concentration of 0.01%.

In a set of experiments designed to determine whether pyrroline dehydrogenase is induced by putrescine and pyrrolidine as in *Pseudomonas* sp. (11), CS101B was grown in various media, and the levels of pyrroline dehydrogenase were assayed. The results presented in Table 4 show that there is no substrate induction of pyrroline dehydrogenase by putrescine or pyrrolidine. (cf. rows 1 and 2). Higher enzyme activities appear in cultures with putrescine and pyrrolidine without ammonia than in cells grown with putrescine, pyrrolidine, and ammonia (rows 2 and 3) due to derepression in response to nitrogen limitation (see also rows 4 and 5 and below).

Catabolite repression. When nitrogen supply is not limited the synthesis of the GABA degradative system in *E. coli* K-12 is strongly repressed by glucose (5). Derepression of the synthesis of the GABA enzymes may be achieved either by substituting a leaner carbon source (such as succinate) for the glucose, or by limiting the supply of nitrogen (5, 28). In Tables 5 and 6 the effects of catabolite repression on the enzymes of the arginine, ornithine, and putrescine degradative pathways are summarized. The synthesis of AUH, PAT, and pyrroline dehydrogenase (PrrD) is very strongly repressed by glucose in the presence of an abundant supply of nitrogen. The repression is relieved by substituting succinate for glucose (Table 5, cf. rows 1 and 2) and is relieved even more by limiting the availability of nitrogen, substituting glycine for the ammonia (Table 5, row 3). In contrast, the synthesis of arginine decarboxylase (ADC) and ornithine decarboxylase (ODC) is neither repressed by glucose nor derepressed by limitation of the nitrogen supply.

TABLE 4. Effect of carbon and nitrogen sources on PrrD formation in strain CS101B

Carbon source[a]	Nitrogen source[b]	Enzyme activity (nmol/min per mg protein)		
		PrrD	GSST	SSDH
Succinate	NH_4^+	960	380	625
Succinate	NH_4^+, putrescine, pyrrolidine	871	361	646
Succinate	Putrescine, pyrrolidine	1,646	625	919
Glucose	NH_4^+	57	75	138
Glucose	GABA	1,926	542	826

[a] Carbon sources were succinate (1.0%) or glucose (0.5%), as indicated.
[b] Nitrogen sources were added to a final concentration of 0.01%, except for $(NH_4)_2SO_4$, which was added to a concentration of 0.1%.

TABLE 5. Effect of catabolite repression and nitrogen availability on enzyme activities in CS101B

Media[a]	Enzyme activity (nmol/min/mg protein)				
	ADC	ODC	AUH	PAT	PrrD
Glucose-NH_4^+	181	182	7	1	57
Succinate-NH_4^+	195	180	194	20	964
Glucose-glycine	177	171	210	36	1,648

[a] Succinate (1%) or glucose (0.5%) served as carbon source; $(NH_4)_2SO_4$ (0.1%) or glycine (0.2%) served as nitrogen source.

Effect of cAMP. The data presented in Table 6 show the effect of cAMP on enzyme synthesis in the arginine, ornithine, putrescine, and GABA catabolic pathways in strain CS101B and in strains with *cya* (21) or *crp* (6) mutations or both. Data on the synthesis of β-galactosidase in the different cultures are given for comparison. Two different patterns may be distinguished. (i) The synthesis of AUH responded to the addition of cAMP to the medium in a manner identical to that of β-galactosidase (4). Growth of the wild-type strain on glucose resulted in repression of AUH synthesis which could be fully relieved by the addition of 10 mM cAMP. In the wild-type strain grown on succinate with no cAMP added, AUH activity was high and increased only slightly when cAMP was added to the growth medium. The Cya^- mutant grown in either glucose or succinate, in the absence of cAMP, showed severely repressed levels of AUH activity. Addition of cAMP to either medium fully relieved the repression. The Crp^- mutant and the Cya^- Crp^- double mutant showed very low AUH activity and did not respond to the addition of cAMP to the growth medium. (ii) The synthesis of PAT and PrrD was also severely repressed by glucose but did not increase significantly on the addition of cAMP to the growth medium. In agreement with these findings and in contrast to AUH, the PAT and PrrD activities of the Cya^- and Crp^- mutants grown in succinate medium with no cAMP were high and did not increase significantly on the addition of cAMP. Catabolite repression of GSST and succinic semialdehyde dehydrogenase (SSDH), the enzymes of GABA catabolism, also exhibited a cAMP-independent component, as has been reported previously (5).

TABLE 7. Enzyme activities in wild-type and *gln* mutant strains

Strain[a]	Media[b]	Enzyme activity (nmol/min per mg protein)				
		AUH	PrrD	PAT	GSST	SSDH
CS101B	Glucose, NH_4^+	16	158	4	200	77
CS101B	Glucose, glutamine	238	1,666	43	442	320
CS101BG	Glucose, NH_4^+	15	217	2	67	ND[d]
CS101BG	Glucose, glutamine	14	225	2	84	27
CS101BC	Glucose, NH_4^+	228	1,466	47	742	ND
CS101BC	Glucose, glutamine	240	1,433	49	522	442

[a] CS101BG is a Gln^- derivative of CS101B; CS101BC is a GlnC derivative of CS101B.
[b] Final concentrations were as indicated: glucose, 0.5%; $(NH_4)_2SO_4$, 0.1%; glutamine, 0.1%.
[c] L-Glutamine (25 μg/ml) was added to CS101BG cultures.
[d] ND, Not determined.

Control by *gln* regulatory genes. That the escape synthesis of the enzymes of GABA catabolism on nitrogen limitation depends on *gln* regulatory elements has been reported previously (28). To see whether the enzymes AUH, PAT, and PrrD were also controlled by the *gln* regulatory system the following experiment was performed. A *gln* mutation that prevents derepression of glutamine synthetase, thus resulting in a glutamine requirement, was introduced by transduction into the wild-type CS101B strain (CS101BG). In parallel, a GlnC (*glnL*) mutation which brings about constitutive derepressed synthesis of glutamine synthetase was introduced into CS101B (CS101BC). The two strains were grown in glucose-ammonia minimal medium (conditions of catabolite repression and nitrogen excess) and in glucose-glutamine medium (conditions of catabolite repression and nitrogen limitation). Strain CS101B with wild-type *gln* alleles served as the control. Substitution of NH_4^+ with glutamine resulted in the release of AUH, PAT, PrrD, GSST, and SSDH from catabolite repression by glucose in

TABLE 6. Effect of cAMP on enzyme synthesis in wild-type, Cya^-, Crp^-, and Cya^- Crp^- strains

Strain[a]	Growth medium[b]	Enzyme activity[c]					
		β-Galactosidase	AUH	PrrD	PAT	GSST	SSDH
CS101B	Glucose-NH_4^+	1.34	11	83	1	162	79
CS101B	Glucose-NH_4^+ + 10mM cAMP	7.38	214	45	1	144	79
CS101By83	Glucose-NH_4^+	1.32	10	71	2	173	185
CS101By83	Glucose-NH_4^+ + 10mM cAMP	7.94	185	24	1	166	197
CS101B Crp^-	Glucose-NH_4^+	1.31	10	120	2	154	268
CS101B Crp^-	Glucose-NH_4^+ + 10mM cAMP	1.27	25	51	2	167	132
CS101By83 Crp^-	Glucose-NH_4^+	1.29	15	80	2	173	161
CS101By83 Crp^-	Glucose-NH_4^+ + 10mM cAMP	1.37	24	46	2	144	232
CS101B	Succinate-NH_4^+	7.72	173	830	22	405	567
CS101B	Succinate-NH_4^+ + 10mM cAMP	8.36	228	781	23	457	670
CS101By83	Succinate-NH_4^+	1.75	14	1,036	20	401	572
CS101By83	Succinate-NH_4^+ + 10mM cAMP	8.75	210	888	27	500	785
CS101B Crp^-	Succinate-NH_4^+	1.75	14	823	23	349	510
CS101B Crp^-	Succinate-NH_4^+ + 10mM cAMP	1.40	12	919	25	359	558
CS101By83 Crp^-	Succinate-NH_4^+	1.51	14	860	23	410	627
CS101By83 Crp^-	Succinate-NH_4^+ + 10mM cAMP	1.58	10	1,001	27	339	734

[a] CS101By83 is a Cya^- derivative of CS101B; CS101B Crp^- is a Crp^- derivative of CS101B; CS101By83 Crp^- is a Crp^- derivative of CS101By83.
[b] Final concentrations were as indicated: glucose, 0.5%; succinate, 1.0%; $(NH_4)_2SO_4$, 0.1%; IPTG was added at 10^{-3} M.
[c] Enzyme activities are expressed as nmol/min per mg of protein, except for β-galactosidase which is expressed as the ratio of the optical density at 420 nm to the optical density at 600 nm.

strain CS101B (Table 7). In strain CS101BG, AUH, PAT, and PrrD were not derepressed on nitrogen limitation. In the constitutive mutant CS101BC, the synthesis of AUH, PAT, and PrrD was derepressed, regardless of the state of nitrogen availability. Data on the synthesis of GABA enzymes are included for comparison.

DISCUSSION

Since the pathway of arginine, ornithine, and putrescine utilization leads to the formation of GABA, it was assumed that this pathway would be controlled by the *gab* regulatory system. However, our results show that a mutation in the regulatory *gabC* locus (strain CS101B) does not affect the arginine-ornithine-agmatine-putrescine degradative pathway. That some interaction between this pathway and the *gab* regulatory system does occur is indicated by the fact that a *gab* mutation that causes a severalfold decrease in the activity of GSST and results in the inability of mutant M-20 to grow on GABA as the sole nitrogen source also reduces the activity of PAT and PrrD.

Our results show that AUH, PAT,and PrrD, but not ADC and ODC, are controlled by catabolite repression and nitrogen availability. In the case of AUH the mechanism of catabolite repression conforms to the classical model involving the cAMP-CAP complex (26), whereas the regulation of PAT and PrrD synthesis, like that of the GABA degradative enzymes, exhibits a cAMP-independent component (Table 6). The escape of AUH, PAT, and PrrD synthesis from catabolite repression under conditions of nitrogen limitation is controlled by the *gln* regulatory genes (Table 7), as in the case of the GABA degradative enzymes (28).

The genes, which code for ADC, AUH, and ODC, *speA*, *speB*, and *speC*, respectively, are clustered at 64 min (3), with *speA* and *speB* being very closely linked to each other (12). It was expected that these three genes would behave as one regulatory unit. However, our results show that this is not the case. AUH responded to induction by L-arginine and agmatine (Table 3), to repression by glucose, and to derepression by nitrogen limitation (Table 5). ADC and ODC synthesis did not respond to any of these controls (Tables 3 and 5). These findings are in agreement with the observation of Hafner and Tabor (9) that bacteriophage Mu insertion into either *speA* or *speB* did not affect the expression of the other gene, indicating that the two genes are not in the same operon.

The results showing a lack of response of ADC and ODC synthesis to different carbon sources for growth differ from the results of Boyle and co-workers (2, 23, 27), who have found that the synthesis of ADC, ODC, and AUH in *E. coli* is actually enhanced in the presence of glucose as the carbon source. The positive effect of glucose, according to Boyle and co-workers, is due to the low level of cAMP in glucose-grown cells. This is in direct contrast with our finding that glucose represses and cAMP derepresses AUH synthesis (Table 6). It is possible that the discrepancy between our results and those of Boyle and co-workers may be explained by differences between the strains used. Indeed, when we tested the *cya* mutant used by Boyle and co-workers, strain CA8303, for its synthesis of ADC and ODC, the latter was repressed by the addition of cAMP, as reported by Wright and Boyle (27), while in the *cya* derivatives of strain CS101B ADC and ODC synthesis was not affected by cAMP. Boyle and co-workers report growth rates of their strains on glucose and succinate that are much slower than those of CS101B and its derivatives. Our *cya* and *crp* derivatives of CS101B grow on succinate somewhat better than the strains used by Boyle and co-workers (doubling time, 3.2 versus 4.8 h). This may be due to secondary mutations that permit better utilization of succinate by CS101B mutants. Nevertheless, the synthesis of β-galactosidase in the *cya* and *crp* derivatives of strain CS101B responds in a classical fashion to repression by glucose and relief of this repression by the addition of cAMP.

Canellakis and associates have recently shown that the activity of ADC and ODC in *E. coli* is inhibited by basic proteins (antizymes), the synthesis of which is induced by polyamines (10). Since ADC and ODC each catalyzes the respective first step in pathways leading to the biosynthesis of polyamines, substances that play an important role in the regulation of the cell cycle, the control of these enzymes by polyamines makes good sense (18, 19).

In summary, the control of the arginine and ornithine degradative pathway in *E. coli* K-12 acts on information on the supply of carbon and nitrogen and the level of polyamines, end products of this pathway, and effectors of the cell cycle. Fine tuning to the different signals is achieved by targeting them to different enzymes of the pathway. Thus, ADC and ODC seem to be exclusively controlled by polyamine levels (10); AUH is the only element regulated by cAMP-CAP-mediated catabolite repression; and PAT, PrrD, and the *gab* enzymes mainly respond to cAMP-independent catabolite repression. In each case, catabolite repression can also be circumvented by activation through the *gln* regulatory system in response to nitrogen limitation.

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