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Induction of the heat shock regulon does not produce thermotolerance in *Escherichia coli*

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The addition of isopropyl thio-β-D-galactoside (IPTG) to *Escherichia coli* cells containing multiple copies of the heat shock regulatory gene *htpR* (*rpoH*) under the control of an IPTG-inducible promoter (P-tac) induced 15 of the 17 polypeptides of the heat shock (HTP) regulon. The time course and magnitude of the induction closely resembled that caused by a shift to 42°C. Nevertheless the two means of inducing the heat shock regulon differed in outcome. Cultures grown at 28°C and induced by incubation at 42°C for 15 min gave significant protection against a challenge temperature of 50°C, but no protection was afforded by a 15-min IPTG treatment at 28°C. It could be shown that there was no interference by IPTG with the development of thermotolerance at 42°C. Also, treatment of a wild strain of *E. coli* with various toxic agents revealed no correlation between the development of thermotolerance and the induction of any subset of the heat shock proteins. Thermotolerance appears to develop by processes other than the *htpR*-dependent induction of heat shock proteins.

[*Key Words:* Heat shock gene expression; heat shock function; thermotolerance; *Escherichia coli*]

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Exposure to temperatures above the range that permits cell growth leads to progressive loss of cell viability in microbial populations and severe developmental abnormalities (including phenocopies, which mimic the effect of various developmental mutants) in higher plants and animals. In both situations it is generally observed that exposure of the organism to moderately elevated temperature for brief periods provides some protection against the lethal or deleterious developmental effects of a subsequent shift to a higher temperature. This acquired thermotolerance has been observed in organisms as diverse as bacteria (Yamamori and Yura 1982), various plants (cited in Altschuler and Mascarenhas 1982), whole mice, Chinese hamsters, *Drosophila* (embryos, larvae, pupae and adults), and cells of higher organisms (including human) in tissue culture (reviewed in Craig 1985 and Lindquist 1986).

It has been widely concluded that thermotolerance develops during brief incubation at elevated but nonlethal temperature as a result of the heat shock response. The evidence consists of extensive correlations between synthesis of heat shock proteins and the development of thermotolerance. For example, in many organisms some chemical treatments (e.g., recovery from anoxia, exposure to ethanol, cadmium chloride, or sodium arsenite) are as effective as mild heat in leading to thermotolerance, and these conditions also induce the synthesis of heat shock proteins. However, there are also reports that thermotolerance can be acquired without induction of heat shock proteins, and that hyperproduction of them does not always produce thermotolerance (reviewed in Craig 1985; Landry 1986; Lindquist 1986).

Particularly because the overall function of the heat shock response is still a matter of speculation, it would be useful to clarify the matter of thermotolerance. Is protection against heat an outcome of the induced synthesis of heat shock proteins? Is the heat shock response sufficient for the acquisition of thermotolerance? Is the heat shock response necessary for the development of thermotolerance?

In *E. coli* the heat shock response is governed by a positive transcription factor, HtpR (σ^{32}) (reviewed in Neidhardt and VanBogelen 1987), and elevation of the cellular level of this factor induces the heat shock regulon (Grossman et al. 1987). With this as a starting point we have examined the relationship between induction of this regulon and the development of thermotolerance. We have found that maximum thermotolerance can be developed by agents that only weakly induce three or four of the 17 heat shock proteins, and that virtually complete induction of the heat shock regulon can occur without the concomitant development of any thermotolerance. These findings indicate that some one or more unknown processes outside the heat shock response are essential to the development of thermotolerance, and that the 17-protein bacterial heat shock response has function(s) other than protection against the lethal effects of high temperature.

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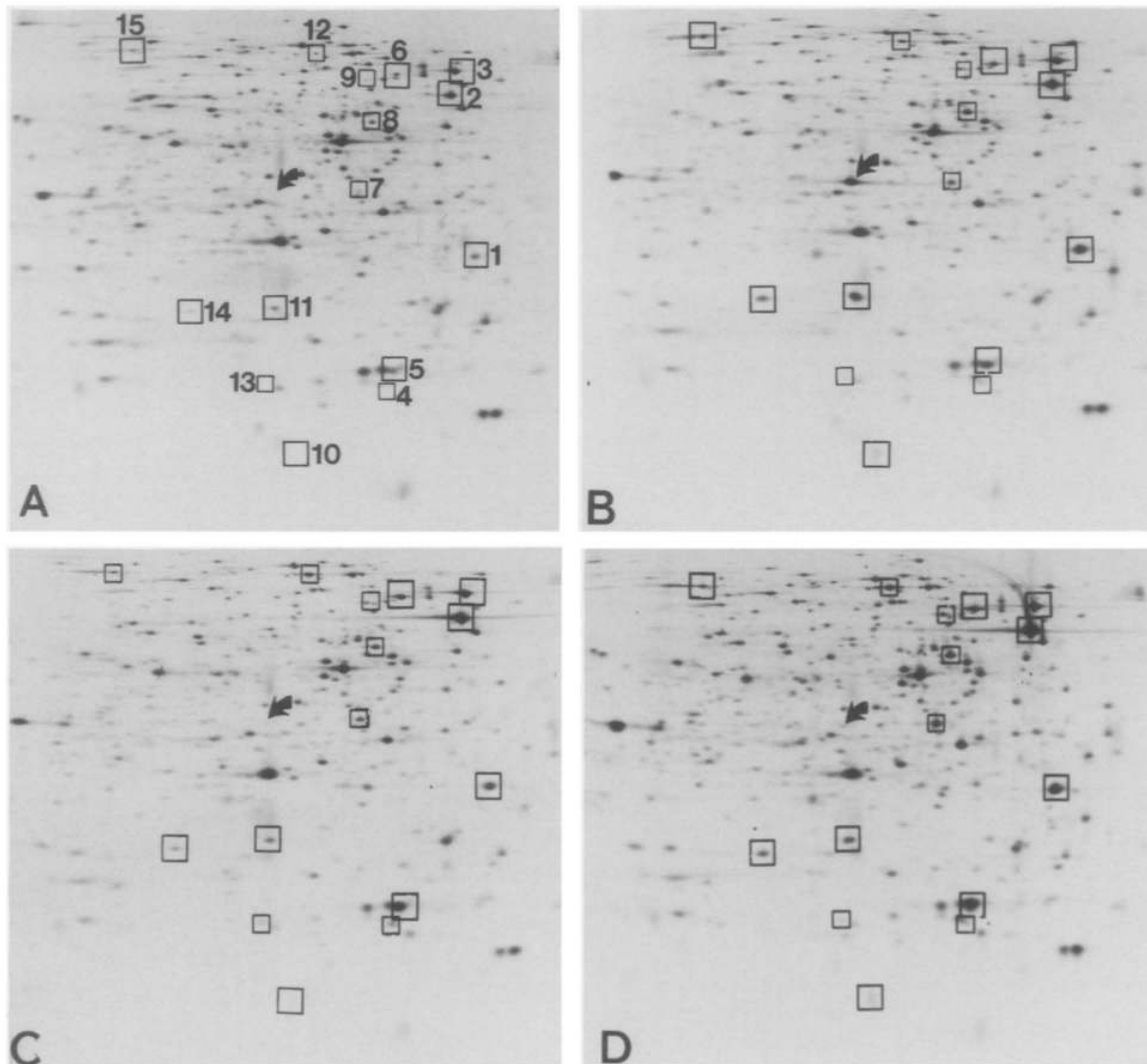

Figure 1. Synthesis of individual proteins resolved on two-dimensional gels from a strain of *E. coli* (CG690) containing the wild-type allele of *htpR* both on the chromosome and fused to P-tac on a plasmid. The autoradiograms show the incorporation of [^{35}S]methionine for 15 min: (*A*) at 28°C; (*B*) at 28°C beginning immediately after addition of IPTG (5 mM); (*C*) beginning immediately after a shift to 42°C; and (*D*) beginning immediately after a shift to 28°C to 42°C of a culture that had been pretreated for 15 min at 28°C with IPTG (5 mM). The arrow indicates the position of the *htpR* gene product, α^{32}. The protein spots in boxes, numbered in *A*, are the heat shock proteins (Neidhardt and VanBogelen 1987): (1) B25.3 (GrpE); (2) B56.5 (GroEL); (3) B66.0 (DnaK); (4) C14.7; (5) C15.4 (GroES); (6) C62.5; (7) D33.4; (8) D48.5; (9) D60.5 (LysU); (10) F10.1; (11) F21.5; (12) F84.1; (13) G13.5; (14) G21.0; (15) H94.0 (Lon). Not shown are σ^{70} and DnaJ.

Results

Induction of the heat shock regulon by IPTG and heat in strains containing htpR *fused to P-tac*

Cultures of *E. coli* strain CG690 were grown at 28°C and then either (1) shifted to 42°C for 15 min, (2) treated wtih IPTG at 28°C for 15 min, or (3) shifted to 42°C for 15 min after pretreatment with IPTG at the lower temperature for 15 min. Each culture was labeled for the 15-min test period with radioactive methionine. Extracts were processed by two-dimensional gel electrophoresis, and autoradiograms were used to examine the pattern of protein synthesis (Fig. 1).

Addition of IPTG at 28°C resulted in a high rate of production of the *htpR* gene product, F33.4 (σ^{32}), and visible induction of all but three of the heat shock proteins (proteins C14.7, D60.5, and G13.5 being the exceptions) seen on two-dimensional gels (cf. Fig. 1A with Fig. 1B). The induction appeared visually to be as intense as that produced by a shift to 42°C (Fig. 1C). The induction of some HTP proteins by a shift to 42°C was somewhat enhanced by preincubation of the cells with IPTG for 15 min at 28°C (cf. Fig. 1 B with Fig. 1D).

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These experiments were repeated with strain CSH26 containing plasmid pDS2 with *htpR* fused to P-tac. The results (not shown) were virtually identical.

Curiously, σ^{32} seemed not to be hyperproduced at 42°C, despite the presence of IPTG (Fig. 1D). This result would be expected if the tac promoter were transiently repressed at high temperature, or if the more rapid degradation reported for σ^{32} at high temperature (Grossman et al. 1987) were sufficient to prevent its accumulation to the level seen at 28°C. These possibilities were examined by labeling the cells in the presence of IPTG at 42°C and then chasing the label with nonradioactive methionine for 0, 1, and 3 min. The results (not shown) indicated that the 3-min chase employed in the experiment of Figure 1 was sufficient to permit degradation of HtpR at this temperature.

To confirm the impression that IPTG induces a nearly normal heat shock response in strain CG690 at 28°C, the experiment presented in Figure 1 was repeated, but with a labeling protocol that permitted quantitative measurement of the synthesis of individual proteins. The results (Table 1) indicate that, of 15 heat shock proteins sampled, 10 were induced by IPTG at 28°C as well as or better than by a shift to 42°C. The exceptions were B56.5 and C15.4 (induced half as well), C14.7 and D60.5 (not induced), F84.1 (induced one-third as well), and G13.5 (induced one-fifth as well). A curious, but reproducible, result was that three heat shock proteins were induced less well by a combination of heat plus IPTG than by IPTG or heat alone.

Table 1. *Induction of proteins in strain CG690 by IPTG and heat*

	Differential rate of synthesis[b]		
Protein[a]	IPTG (28°C)	42°C	IPTG (28°C and 42°C)
B25.3 (GrpE)	5.11	2.22	3.76
B56.5 (GroEL)	2.65	5.71	7.90
B66.0 (DnaK)	3.99	2.95	3.35
C14.7	1.25	6.56	1.85
C15.4 (GroES)	2.75	3.97	7.91
C62.5	5.70	7.84	11.8
D33.4	5.73	6.45	9.86
D48.5	5.40	2.65	1.17
D60.5 (LysU)	0.87	2.37	3.86
F10.1	7.40	2.46	3.56
F84.1	4.90	14.1	28.6
F21.5	3.78	1.17	1.36
G13.5	3.38	18.0	3.02
G21.0	5.14	2.65	2.75
H94.0 (Lon)	4.09	3.00	3.19
Control:			
E42.0 (EF-Tu)	0.91	0.84	0.78

[a]Proteins and their identifications are described in Neidhardt and VanBogelen (1987).
[b]The differential rates of synthesis are based on 15-min incorporation periods, as described in Materials and methods, and are expressed relative to the differential rates of synthesis during steady-state growth at 28°C in the absence of IPTG. IPTG (28°C), labeling was from 0 to 15 min after addition of IPTG (5 mM) to a culture in steady-state growth at 28°C; 42°C, labeling was for 0–15 min after shifting a culture from steady-state growth at 28°C to 42°C; IPTG (28°C and 42°C), labeling was from 0 to 15 min after shift of a culture to 42°C that had received IPTG (5 mM) 15 min earlier during steady-state growth at 28°C.

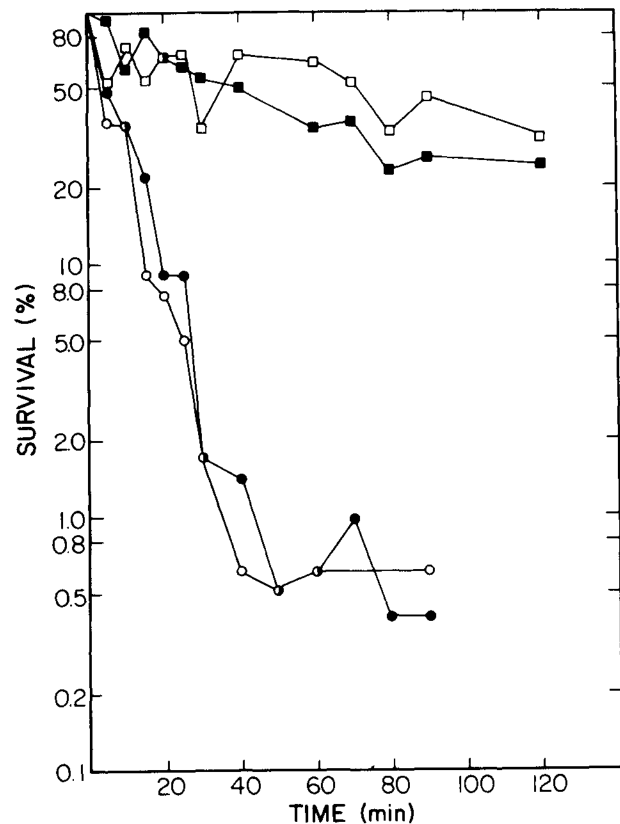

Figure 2. Induction of thermotolerance to 50°C in *E. coli* strain CG690 containing the wild-type allele of *htpR* both on the chromosome and fused to P-tac on a plasmid. Cultures were grown in glucose-rich medium at 28°C and shifted to the challenge temperature of 50°C after: no treatment (●), treatment with IPTG (5 mM) for 15 min at 28°C (○); treatment for 15 min at 42°C (■); and treatment consisting of incubation with IPTG (5 mM) for 15 min at 28°C and 15 min at 42°C (□). Duplicate samples of each culture were diluted and plated at 30°C to determine the number of viable cells at each time point. The experiment was typical of several done at slightly different challenge temperatures.

Effect of IPTG and incubation at 42°C on thermotolerance

Strain CG690 was grown in glucose-rich medium at 28°C, and subcultures were treated as described in Figure 1 to induce the HTP regulon. These cultures were then exposed to the lethal temperature of 50°C, and the loss of viability was followed by plate counts.

Incubation at 42°C, with or without prior addition of IPTG for 15 min at 28°C, induced thermal protection as usual, but induction of the HTP regulon by IPTG at 28°C failed to provide any protection at all (Fig. 2). The same results were obtained using the other *htpR* fusion plasmid, pDS2, in strain CSH26.

The failure of IPTG to induce thermotolerance could be explained if the heat shock proteins induced at 28°C

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by IPTG require some sort of activation that can occur at 42°C but not at 28°C. To test this possibility the cells were treated with IPTG at 28°C for 15 min, then shifted to 42°C with the simultaneous addition of chloramphenicol to block protein synthesis. After 15 min the cells were shifted to 50°C and viability was followed. The treatment at 42°C failed to alter the susceptibility of the cells to heat (results not shown).

Effects of ethanol, puromycin, H_2O_2, $CdCl_2$, amino acid starvation, and nalidixic acid

The failure of IPTG to induce thermotolerance could conceivably have been the result of failure to induce heat shock proteins C14.7 and D60.5, or the failure to achieve some critical level of one or more of the other three poorly induced heat shock proteins. To explore these possibilities, we examined thermotolerance in cells subjected to a number of treatments previously used in a study of induction of the heat shock response (VanBogelen et al. 1987). These treatments vary widely in the number of heat shock proteins they induce, and in the magnitude of the inductions (Table 2).

The results (Fig. 3) were that exposure to ethanol and to $CdCl_2$ for 15 min, and to H_2O_2 for 60 min, led to the same degree of protection to a challenge at 50°C as did incubation at 42°C for 15 min, while exposure to nalidixic acid, to puromycin, to valine, and to H_2O_2 for 15 min led to no protection. Combined with the information in Table 2, these results indicate that thermotolerance can develop in response to chemical treatments that induce fewer than half of the heat shock proteins. Also, since proteins C14.7, D60.5, and G13.5 were induced by at least one agent (puromycin or nalidixic acid) that did not produce thermotolerance, and failed to be induced by one agent (H_2O_2) that did produce thermotolerance, the failure of the IPTG-induced heat shock response to confer thermotolerance seems unrelated to failure to induce these three proteins.

Discussion

As expected from the work of others (Grossman et al. 1987; C. Georgopoulos, pers. comm.), overproduction of σ^{32} from an *htpR* gene fused to P-tac induced the synthesis of heat shock proteins. To permit physiological assessment of the function of this response, it was necessary for us to examine synthesis of each of the heat shock proteins following IPTG addition. The two independent constructions of P-tac–*htpR* yielded similar results—heat shock proteins were induced in number and magnitude similar, but not identical, to what occurs upon shift to 42°C (Table 1).

Since no thermotolerance was generated by the IPTG-induced response at 28°C (Fig. 2) (even after allowing incubation at 42°C in the absence of protein synthesis), one must conclude that the bacterial heat shock response does not produce thermotolerance, or else that the few differences between IPTG induction and heat induction of heat shock proteins are crucial.

The latter possibility is rendered unlikely by several observations. The poorest inductions by IPTG relative to heat were those of proteins C14.7, D60.5, and G13.5. These proteins were also not induced by H_2O_2 treatment for 60 min, yet thermotolerance developed; two of them (C14.7 and G13.5) were induced by puromycin treatment and the third by nalidixic acid, neither of which treatments produce thermotolerance. Furthermore, a particular mutant strain that has been found not to produce C14.7 and G13.5 at 44°C does develop thermotolerance at this temperature (R.G. Matthews, this laboratory, unpublished). Although proteins B56.5, B66.0, and F84.1 were induced less well by IPTG than by heat, IPTG treatment was as effective as, or more effective than, three other treatments which did bring about thermotolerance: ethanol, $CdCl_2$, and H_2O_2 (for 60 min).

Though they seem irrelevant to thermotolerance, the differences in induction of heat shock proteins by the three treatments used here are interesting. Speculation about the independent behavior of individual heat shock proteins (observed previously as well; VanBogelen et al.

Table 2. *Induction of thermotolerance and individual heat shock proteins in* E. coli *strain W3110*

Treatment[a]	Thermo-tolerance[b]	Relative increase in level of heat-shock proteins[c]														
		B25.3	B56.5	B66.0	C14.7	C15.4	C62.5	D33.4	D48.5	D60.5	F10.1	F21.5	G13.5	G21.0	F84.1	H94.0
Shift to 42°C	yes	++	++	++	++	++	++	++	+	+	+	+	+	+	++	++
Ethanol	yes	++	++	++	++	++	++	++	+	+	+	+	+	+	++	++
$CdCl_2$	yes	++	0	+	++	0	+	0	0	0	0	0	+	0	+	0
H_2O_2 (60 min)	yes	0	0	0	0	0	+	0	0	0	0	0	0	0	0	0
Puromycin	no	++	0	0	+	+	0	0	0	0	+	+	+	0	0	0
Nalidixic acid	no	+	+	+	0	+	0	+	0	+	0	0	0	+	+	0
H_2O_2 (15 min)	no	+	0	+	0	+	0	0	+	0	0	0	0	0	0	0
Ile restriction	no	0	0	0	0	+	0	0	0	0	0	0	0	0	+	0

[a]Treatments are described in the legend to Figs. 2 and 3.
[b]Thermotolerance was scored "yes" if the treatment resulted in a killing rate similar to that obtained when the culture is treated at 42°C for 15 min prior to challenge at 50°C, and "no" if the rate of killing was similar to an untreated culture (Figs. 2 and 3).
[c]Relative increases were measured as described in Materials and methods. Relative to the differential rate of synthesis at 28°C, ++ indicates an increase >10-fold, + indicates an increase from 2- to 10-fold, and 0 indicates no detectable increase. The individual heat shock proteins are described in Neidhardt and VanBogelen (1987).

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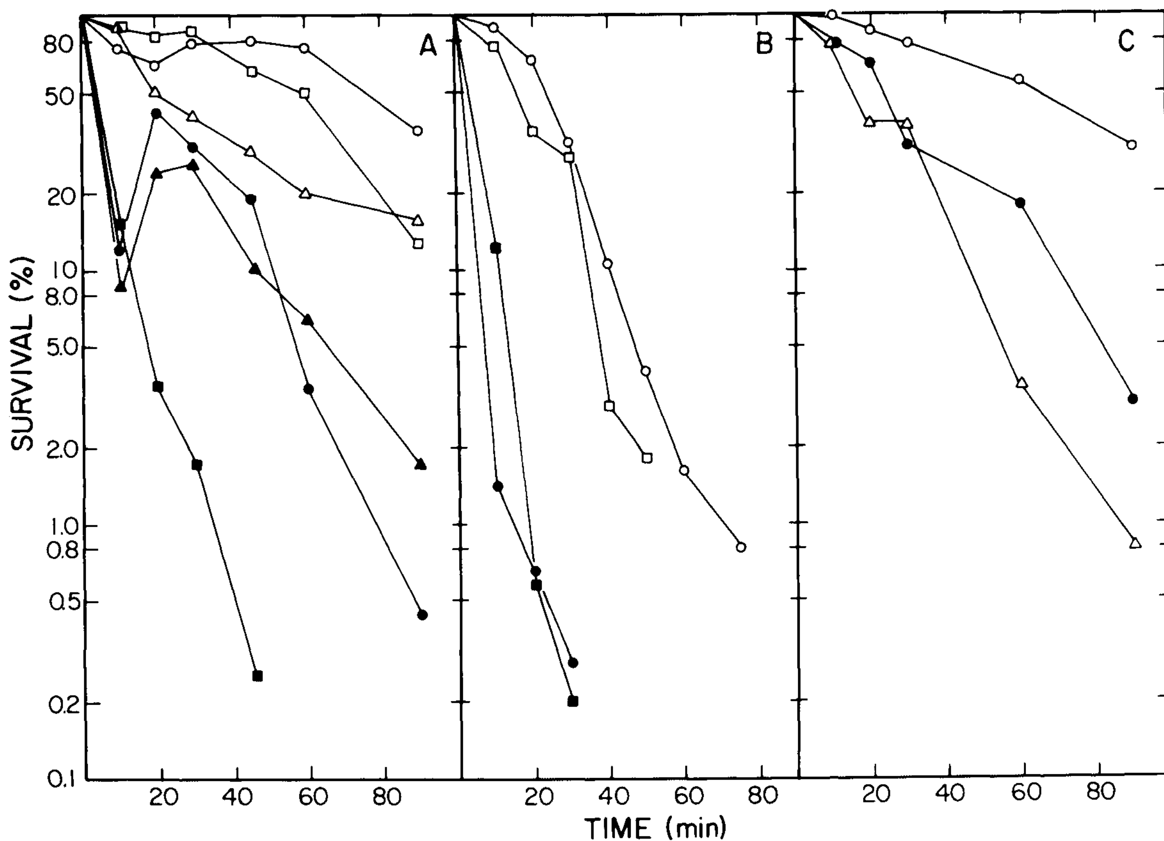

Figure 3. Induction of thermotolerance to 50°C in *E. coli* strain W3110 after various treatments. Cultures were grown in glucose-rich medium (*A* and *B*) or glucose minimal medium (*C*) at 28°C and then after different treatments (all for 15 min at 28°C unless otherwise specified) were exposed to the challenge temperature of 50°C with 4000-fold dilution of the toxic chemicals. The cultures in *A* received: no treatment (●); 42°C (○); ethanol (10%) (□); $CdCl_2$ (600 μM) (△); nalidixic acid (172 μM) (▲); and puromycin (200 μg/ml) (■). In *B* the cultures received: no treatment (●); 42°C (○); H_2O_2 (70 μg/ml) (■); and H_2O_2 (70 μg/ml) for 60 min (□). In *C* the cultures received: no treatment (●); valine (3.4 mM) to restrict for isoleucine (△); and 42°C (○). Duplicate samples of each culture were diluted and plated at 30°C to determine the number of viable cells at each time point. Differences in the degree of thermotolerance developed at 42°C reflect the variation in killing in different experiments as a result of slight differences in temperature or the use of different media or strains; controls (no treatment and treatment at 42°C) were always run under identical conditions as the experimental treatments.

1987) is premature until more is known of their promoter structures and their mechanisms of control.

If the heat shock response does not produce thermotolerance, what does?

We propose that there are two distinct, inducible states of *E. coli*: thermotolerance and heat shock. Thermotolerance is a state of resistance to thermal killing, and results from some unknown cellular processes that occur outside the σ^{32}-related heat shock response. The processes leading to thermal protection are triggered by such agents as moderate heat, ethanol, $CdCl_2$, and prolonged treatment by H_2O_2. Possibly, the production of some selected heat shock proteins is necessary for protection against lethal temperature, although the results with H_2O_2 treatment (Table 2) make even this limited possibility unlikely.

The second state, heat shock, is brought about by a σ^{32}-dependent induction of 17 or so proteins, and we propose that this state is necessary for cellular adjustment to growth at elevated (nonlethal) temperature. We have previously suggested cell division as one of the processes requiring the heat shock response for adaptation to growth upon a shift up in temperature (Tsuchido et al. 1986).

Heat, in this scheme of things, is an inducer of two different states, and it is likely that the heat shock state may be necessary for thermal protection only in the case of heat-induced (rather than toxic chemical-induced) thermotolerance.

This interpretation of our results is not in conflict with existing information about thermotolerance development in other organisms. The evidence supporting a necessary and sufficient role of the heat shock response in thermotolerance is based on temporal correlation of the synthesis of heat shock proteins and the development of thermotolerance (reviewed in Lindquist 1986; Landry 1986). Though instances of this correlation are extensive, such evidence alone cannot establish a causal relation, and are readily accounted for by our proposal.

Furthermore, the literature contains numerous examples in a wide variety of organisms in which the development of thermotolerance appeared unrelated to the

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induced synthesis of heat shock proteins (reviewed by Lindquist 1986; Landry 1986). Contradictions of this sort are what one would expect if thermotolerance were a different state than heat shock, though induced by some of the same agents.

The interpretation that heat shock and thermotolerance are separable, though related, phenomena has been reached by others (e.g., Landry and Chretien 1983; reviewed by Landry 1986), and is not far different from the views expressed by Lindquist (1986).

Our findings, and this interpretation of them, highlight the need for a search in *E. coli* for some process outside the heat shock regulon for the development of thermotolerance. Also, if heat shock proteins are at best only indirectly concerned with the development of thermotolerance, the main function of the heat shock response must be with other matters.

These results have implications for eukaryotic systems, not because one would necessarily expect thermotolerance to depend on the same processes from bacteria to humans, but because the evidence that increased synthesis of heat shock proteins protects embryos of *Drosophila* (Petersen and Mitchell 1982) and rats (Walsh et al. 1985) from thermally induced developmental abnormalities is formally similar to the evidence that had implicated the heat shock regulon of *E. coli* in thermotolerance. Likewise, efforts to maintain the heightened adjuvant thermal sensitivity of cancer cells for therapeutic purposes (reviewed in Hahn 1982; Gerner 1983; Landry 1986; Li and Mivechi 1986) should take into account the possibility that processes outside the synthesis of heat shock may be involved in thermotolerance.

Materials and methods

Bacterial strains and plasmids

All bacterial strains used were K-12 type *E. coli*. Strain W3110 is prototrophic (Smith and Neidhardt 1983). Strain CG690 (kindly provided by Costa Georgopoulos) contained plasmid pTH, which carries a *Hin*dIII–*Pvu*I fragment containing the *htpR* gene linked to the *tac* promoter (K. Tilly and C. Georgopoulos, unpubl.). Strain CSH26 (Miller 1972) contained plasmid pDS2, which also carries the *htpR* gene linked to the *tac* promoter as previously described (Grossman et al. 1987).

Media and growth conditions

Cultures were grown aerobically in rotary action H_2O incubator shakers at the indicated temperature. Liquid MOPS medium (Neidhardt et al. 1974) was supplemented with glucose (0.4%) and thiamine (10 μM) for minimal medium or with glucose (0.4%), 20 amino acids, and 5 vitamins (Wanner et al. 1977) for rich medium.

Radioactive labeling of protein and resolution on two-dimensional gels for autoradiography

Cultures were grown in rich medium (with methionine reduced to 0.015 mM) to an $OD_{420\ nm}$ of 0.3. A 2-ml sample was labeled for 15 min by the addition of [^{35}S]methionine (1097 Ci/mmole) to a final concentration of 50 μCi/ml, and chased for 3 min with nonradioactive methionine (17 mM). Extracts were prepared and processed for resolution on two-dimensional polyacrylamide gels (O'Farrell 1975) as previously modified (Blumenthal et al. 1976). Gels were stained with Coomassie Brilliant Blue R and exposed to Kodak XAR film for 3 days.

Measurement of rates of synthesis of individual proteins

Cultures were grown in glucose-rich medium (with methionine reduced to 0.015 mM) and portions (2 ml) were labeled for 15 min before and after treatment with IPTG and/or a temperature shift by adding [^{35}S]methionine (1097 Ci/mmole) to a final concentration of 100 μCi/ml. Nonradioactive methionine (17 mM) was added for a 3-min chase. To each sample was added a portion of a culture of the same strain grown in ^{3}H-labeling medium consisting of glucose-rich medium containing [^{3}H]leucine (4.8 mCi/mmole, 100 μCi/ml) and with the isoleucine and valine reduced to 40 and 60 μM, respectively (one-fifth the usual concentrations). The mixed sample was then sonicated to prepare a cell extract for resolution on two-dimensional gels. An autoradiogram was prepared to permit visualization of the ^{35}S-labeled proteins. Protein spots chosen for quantitative assay were sampled from the gel with a syringe needle and processed as previously described (Pedersen et al. 1976) to permit measurement of their ^{35}S and ^{3}H content by scintillation counting. The differential rate of synthesis of a sampled protein was defined as the $^{35}S/^3H$ ratio of the sampled spot divided by the same isotope ratio of the unfractionated mixed extract.

Measurement of viable cells after exposure to lethal temperature

Cultures were grown in rich medium (except for isoleucine restriction, which was accomplished by adding 400 μg/ml of valine to minimal medium) to $OD_{420\ nm}$ of 0.3 before initiation of treatment. After cultures were exposed to IPTG (5 mM), ethanol (10%), nalidixic acid (40 μg/ml), $CdCl_2$ (600 μM), H_2O_2 (70 μg/ml), 42°C, or 42°C and chloramphenicol (50 μg/ml) for 15 min, or to H_2O_2 for 60 min, the cultures were diluted 1 : 4000 and shifted to 50.4 ± 0.15°C. Samples (0.1 ml and 0.025 ml) taken immediately before the shift to 50°C and at various times after the shift were plated on Luria broth plates and incubated at 30°C overnight. Because of variability from day to day (e.g., Figs. 2 and 3), untreated controls were always run in each experiment, and all experiments were performed a minimum of three times.

Acknowledgments

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Note added in proof

We noted only recently work with *Tetrahymena thermophila* (Hallberg, R.L., *Mol. Cell. Biol.* **6:** 2267–2270, 1986) leading to conclusions similar to ours.

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