The Induction of Urea Carboxylase and Allophanate Hydrolase in Saccharomyces cerevisiae*

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SUMMARY

Saccharomyces cerevisiae can utilize urea as a sole nitrogen source; this compound is degraded to CO₂ and NH₃ by a multienzyme complex (WHITNEY, P. A., AND COOPER, T. G. (1972) Biochem. Biophys. Res. Commun. 49, 45) composed of urea carboxylase and allophanate hydrolase. Since these activities are present in cultures grown in media containing urea, arginine, or a purine base, the nature of the inducer was investigated. The data presented here indicate that it is the intermediate compound, allophanate, which is the inducer of both urea carboxylase and allophanate hydrolase. This conclusion is based on the observation that: (a) urea induces both activities in a wild type strain, (b) urea has no effect on the basal levels of allophanate hydrolase produced by mutants lacking urea carboxylase, and (c) urea has no effect on the high constitutive level of urea carboxylase produced by a mutant lacking allophanate hydrolase. Consistent with this view is the observation that a urea analogue, formamide, cannot induce allophanate hydrolase in a strain lacking urea carboxylase activity, whereas an allophanate analogue, hydantoic acid, is able to serve as an inducer in such a strain. Both of these compounds are able to effect the induction of both activities in a wild type strain. Mutants blocked in either arginase or urea carboxylase were also used to show that the derepression of allophanate hydrolase following the onset of nitrogen starvation is, in fact, internal induction, and is contingent upon the ability of the cells to produce the inducer, allophanate, from internal arginine and urea pools.

The yeast, Saccharomyces cerevisiae, is capable of using urea as its sole nitrogen source. Whitney and Cooper (1) have shown that this capability depends on the presence of a urea-degradative multienzyme complex. This complex is composed of biotin-containing urea carboxylase and allophanate hydrolase catalyzing reactions 1 and 2, respectively (2).

1 Urea + ATP + HCO₃⁻ → allophanate + ADP + P₁ (1)
2 Allophanate → 2 CO₂ + 2 NH₃ (2)

Mutants deficient in each of these enzymes have been isolated (2) and the mutant alleles have been shown to be linked. Thus, the urea-degradative system in yeast appears to possess a biochemical and genetic organization similar to those of a number of biosynthetic pathways containing enzyme aggregates in both yeast and Neurospora (3-5). Since it can be shown that the components of the urea-degradative system are organized together both biochemically and genetically, it is reasonable to inquire whether these components are also regulated together. This inquiry was pursued by investigating the nature of the inducer of these two enzymes. The data presented here show that allophanate, the product of the urea carboxylase reaction, is the inducer of allophanate hydrolase and, most likely, the inducer of urea carboxylase also. It will be shown that analogues of urea can serve as nonmetabolizable inducers of the system only if they can be carboxylated, but that such carboxylation is not required for induction by the nonmetabolizable allophanate analogue, hydantoic acid. Finally, we shall present results obtained through the use of these nonmetabolizable inducers; they indicate that the apparent derepression of the urea-degradative system under conditions of nitrogen starvation is contingent upon the presence of the inducer in the cells. A preliminary account of this work has already appeared (6).

MATERIALS AND METHODS

Strains—M-25, a wild type diploid strain of S. cerevisiae, and the mutant strains derived from it have been described previously (2). M-62, M-64, and M-56 are diploid mutant strains lacking urea carboxylase, allophanate hydrolase, and arginase activities, respectively (7). Each mutant strain is homozygous for the significant allele.

Culture Conditions—In order to ascertain the effect of various physiological situations upon the rate of synthesis of the urea-degrading enzymes, cells were grown in minimal medium (2) containing 0.6% glucose and 0.02% (NH₄)₂SO₄, and the growth was monitored as optical density in a Klett-Summerson photomicrograph.
electric colorimeter. A culture with a density of 100 Klett units contains approximately 2 x 10^7 cells per ml. Induction of the urea-degrading enzymes was initiated by addition of urea or one of the analogues at the indicated concentrations. At appropriate times, thereafter, 10-ml samples of the induced cultures were transferred to a tube containing sufficient cycloheximide to give a final concentration of 10 μg per ml and rapidly cooled to 0°. The chilled cells were collected by centrifugation. After resuspension of the cells in 0.5 ml of 0.05 M Tris, pH 7.9, containing 5% glycerol, 2.0 x 10^{-4} M EDTA, and 3.0 x 10^{-4} M mercaptoethanol, the cells were rendered permeable with the method of Ramos et al. (8), with the exception that the procedures were carried out at 0°.

**Assay Conditions**—The enzymes of the urea-degradative system were determined using assay conditions similar to those reported earlier (Table I of Ref. 2). Since it is not presently possible to measure urea carboxylase activity in whole cell preparations containing allophanate hydrolase, it was necessary to use the complete, urea amido-lyase, activity as a measure of urea carboxylase activity. The coupling of the urea carboxylase reaction to that of allophanate hydrolase in wild type cells is reasonable since if the actual in vivo levels of these enzymes are compared under various conditions, a large excess of the hydrolase is always found. In strains lacking allophanate hydrolase activity, urea carboxylase could be measured directly as the production of [14C]allophanate from [14C]urea. The reaction mixture was identical with that used in the urea amido-lyase reaction (Table I of Ref. 2). The reaction was terminated by the addition of an equal volume (1.0 ml) of absolute ethanol; the salt concentration was lowered by the addition of 2.0 ml of water and the entire mixture was applied to a Biores-5 column, 0.5 x 2.5 cm. Urea was eluted by four 1.0-ml washes of 1.0 x 10^{-4} M Tris, pH 7.9, containing 20 mM NH_4HC0_3. The allophanate which was adsorbed to the column could then be removed by three 1.0-ml washes with 1.0 x 10^{-4} M Tris buffer, pH 7.9, containing 0.5 mM NH_4HC0_3. Aquasol was added to the eluent and the radioactivity was determined in the scintillation counter. In a control experiment, 94% of the allophanate was retained by the column and could then be eluted under these conditions. Biores-5 (an intermediate base resin containing tertiary and quaternary amine groups) was prepared by successive washings with 8 volumes of 1.0 M KHC0_3 in 0.01 M Tris, pH 7.9, 8 volumes of 1.0 M NH_4HC0_3 in 0.01 M Tris, pH 7.9, and 8 volumes of 20 mM NH_4HC0_3 in 1.0 x 10^{-4} M Tris, pH 7.9.

**RESULTS**

**Nature of Inducer of Urea Carboxylase and Allophanate Hydrolase**—Urea carboxylase and allophanate hydrolase, the two components of the multienzyme complex responsible for the degradation of urea, are found in cells grown in the presence of urea, arginine or allantoin (9), but not in cells utilizing ammonia as the sole nitrogen source. We have shown that the induction of the urea-degradative system observed following addition of arginine (10) depends upon the degradation of this compound to urea. We, therefore, concluded that the presence of urea was necessary for the induction of urea carboxylase and allophanate hydrolase. In order to examine this conclusion more carefully, mutant strains were used in conjunction with the wild type to study the induction of urea carboxylase and allophanate hydrolase individually.

The differential rate of synthesis of allophanate hydrolase in the presence and absence of added urea is shown in Fig. 1A. The addition of urea resulted in about a 5-fold induction over the basal level. When the same experiment was performed with a mutant devoid of urea carboxylase activity (Fig. 1B), however, urea was no longer able to serve as an inducer of allophanate hydrolase; in both the presence and absence of urea the mutant cells contained only basal levels of this activity. Urea was also not able to serve as an inducer of allophanate hydrolase in a second independently isolated mutant possessing a defective urea carboxylase. In a similar type of experiment, urea was used as an inducer of urea carboxylase. As shown in Fig. 2A, addition of urea to a wild type culture elicited a significant induction of this activity. However, when a strain lacking allophanate hydrolase was used (Fig. 2B) urea carboxylase was produced at levels similar to those found in induced wild type cultures, whether or not urea was present in the culture medium.

In an analogous set of experiments, each of the three strains just described was grown on minimal medium; at a cell density of 30 Klett units, one culture of each strain received urea, while a second culture received no inducer. One generation later, at 60 Klett units, all of the cultures were assayed for urea carboxylase and allophanate hydrolase activity. As shown in Table I the amounts of urea carboxylase and allophanate hydrolase in the mutants lacking these activities are significantly below the basal levels; this is consistent with the assumption that these are structural gene mutations. Here, as in Fig. 1, urea was incapable of eliciting the induction of allophanate hydrolase in a carboxylase minus strain and, in a hydrolase minus strain the level of urea carboxylase activity was independent of added urea (Fig. 2). The conclusion suggested

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2 R. Lawther and T. G. Cooper, manuscript in preparation.
The wild type strain, M-25, was grown to a density of 30 Klett units as indicated in the legend to Table 1. The indicated compounds were added to a final concentration of $1.0 \times 10^{-2}$ M and one generation later the cells were harvested and the level of urea amidolyase determined as described under "Materials and Methods."

### Table I

**Production of urea carboxylase and allophanate hydrolase in wild type and mutant strains of Saccharomyces cerevisiae**

The cells were grown to a density of 30 Klett units in minimal medium containing ammonium as the sole nitrogen source. Urea was added to a final concentration of $1.0 \times 10^{-2}$ M where indicated and the cultures were incubated until the cell density reached 60 Klett units. Allophanate hydrolase was determined as [ureido\-\[^4C\]allophanate-dependent $^{14}$CO$_2$ production; urea carboxylase was determined as [ureido-\[^4C\]urea-dependent production of $^{14}$CO$_2$ (M-25 and M-62) or [rdC]allophanate. The activities are expressed as nanomoles per min per ml of culture at 60 Klett units.

| Strain | Urea addition | Amount of substrate cleaved per min per ml of culture (60 Klett units) |
|--------|---------------|---------------------------------------------------------------------|
|        |               | Urea carboxylase | Allophanate hydrolase |
|        |               | nanomoles        | nanomoles             |
| M-25   | +             | 0.70             | 3.8                   |
|        | -             | 0.056            | 0.53                  |
| M-62   | +             | <0.001           | 0.54                  |
|        | -             | <0.001           | 0.62                  |
| M-64   | +             | 0.36             | <0.005                |
|        | -             | 0.43             | <0.005                |

by these data is that allophanate is the inducer of both urea carboxylase and allophanate hydrolase. In the mutant lacking urea carboxylase activity, urea cannot be converted to allophanate, and therefore, is unable to induce allophanate hydrolase. In the mutant lacking allophanate hydrolase activity, allophanate accumulates even in the absence of added urea and induces urea carboxylase to a high level. This conclusion requires the assumption that cells growing in minimal medium contain an endogenous source of urea; presumably this could be arginine.

**Nonmetabolizable Inducers of Urea-degradative Enzymes**

In order to find a nonmetabolizable inducer of the urea degradation system, the wild type strain was grown on minimal medium with ammonia as sole nitrogen source and several analogues of urea and allophanate were added to the cultures; after one generation, the cells were harvested and the level of urea amidolyase was determined. As shown in Table II, urea and the urea analogues formamide, and formyl urea, were able to serve as inducers. Hydantoic acid, an allophanate analogue, was also an inducer, but a poor one.

The level of induction as a function of inducer concentration was determined for urea, formamide, and hydantoic acid. In each case, inducer at the indicated concentration (Fig. 3) was added to cells growing exponentially on minimal medium and the level of enzyme was determined one generation later. As shown in Fig. 3A, urea is a good inducer and maximal induction was achieved at a concentration of $10^{-1}$ M. It is possible, however, that maximum induction may be achieved at an even lower concentration of urea, because at the lower concentrations of inducer it is likely that the supply of urea in the media is exhausted before the completion of the experiment. The urea analogue, formamide, was also a reasonably good inducer (Fig. 3B). The unusual shape of this curve is not understood at this time. One possible explanation is that formamide was not taken up by the cells as well as urea. Hydantoic acid was a relatively poor inducer (Fig. 3C), but it is clear that the addition of this compound did result in an increase in enzyme level.

If the strains used in these studies do not readily take up the formamide and hydantoic acid from the medium then this inability should be reflected in the kinetics of induction of allophanate hydrolase by these compounds. The kinetics of induction of allophanate hydrolase by urea is shown in Fig. 4A; a sharp increase in the rate of enzyme production follows a brief lag. When the analogues, formamide and hydantoic acid were used in place of urea (Fig. 4B), it was found that the lag was somewhat longer in the case of formamide and still longer in the case of hydantoic acid. Although the increased length of the lag again suggests that the cells have difficulty in accumulating these compounds, it is clear that the addition of either analogue

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\text{Induction of ATP-urea amidolyase}
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The wild type strain, M-25, was grown to a density of 30 Klett units as indicated in the legend to Fig. 1. The indicated compounds were added to a final concentration of $1.0 \times 10^{-2}$ M and one generation later the cells were harvested and the level of urea amidolyase determined as described under "Materials and Methods."

| Inducer   | Amount of urea cleaved per min per ml of culture (60 Klett units) |
|-----------|---------------------------------------------------------------------|
| None      | 0.020                                                               |
| Urea      | 0.426                                                               |
| Formamide | 0.484                                                               |
| Hydantoic acid | 0.087                                                         |
| Acetamide | 0.052                                                               |
| Formyl urea | 0.380                                                          |
Fig. 3. Allophanate hydrolase production as a function of inducer concentration. PVI-25 was grown to a density of 30 Klett units in minimal medium containing ammonia as the sole nitrogen source. The inducers were added to the cultures at the indicated molar concentrations, and one generation later the cells were harvested and the levels of allophanate hydrolase were determined. The inducers used were urea (A), formamide (B), and hydantoic acid (C).

resulted in a significant increase in the rate of enzyme production.

When examining the induction of enzymes by analogues, it is necessary to examine the metabolism of the analogues by the cells. From the structures of formamide and hydantoic acid, it is reasonable to expect that any degradation of these compounds would lead to the production of ammonia. Therefore, three cultures were grown on minimal medium containing urea, formamide, or hydantoic acid as the sole source of nitrogen. As shown in Fig. 5, urea was able to serve as the sole nitrogen source, but neither formamide nor hydantoic acid was able to support growth when provided as the only nitrogenous compound. This indicates that neither of these compounds was degraded to ammonia.

Although failure of the cells to utilize formamide suggests that it is not degraded by this yeast, the fact that the inducer of the urea degradation system is allophanate leads to the expectation that this urea analogue is carboxylated. Consistent with this expectation, Whitney and Cooper (11) have shown that formamide is able to substitute for urea in the urea-dependent cleavage of ATP. In addition, formyl urea and acetamide, the other urea analogues able to induce urea amidolyase (Table II), have been shown to support this ADP production in the absence of urea suggesting that these compounds are also carboxylated. Recently, it has been possible to show this carboxylation directly (11). These data suggest the contentions that the urea analogues capable of serving as inducers are carboxylated by urea carboxylase and suggest that the carboxylated products are responsible for the induction of the urea degradation system.

If in fact this conclusion is correct then analogues of urea should not induce allophanate hydrolase in a urea carboxylase-defective strain. This was tested by determining the level of allophanate hydrolase following incubation of a urea carboxylase-defective strain. As shown in Table III, in the case of the compounds, forming as inducer for the wild type, was effective in the carboxylase-defective strains. This is the predicted result for urea and the urea analogue formamide, and indicates that the induction by these compounds is contingent upon their carboxylation by urea car-
boxylase. Since we demonstrated in Fig. 4 that there is a long lag before the onset of allophanate hydrolase induction when hydantoic acid is used as an inducer, the urea carboxylase-less mutant strain (M-62) was grown on minimal medium and the indicated compounds were added at a sufficiently low cell density that when the cells were harvested the inducer had been present in the cultures for 2.5 to 3 generations instead of one generation as in the previous experiments. As shown in Table IV under these conditions hydantoic acid was able to induce allophanate hydrolase approximately 2-fold in the mutant strain. Although the addition of urea and formamide resulted in a slight increase in enzyme level, it should be noted that these levels are significantly below the level found in the culture which received hydantoic acid, whereas in all other experiments the levels found in cultures containing urea or formamide were severalfold higher than those found in cultures containing hydantoic acid. These data show that the urea analogue formamide must be carbonylated by urea carboxylase in order to serve as an inducer of allophanate while the allophanate analogue, hydantoic acid, is able to serve as an inducer even in the absence of urea carboxylase activity. These data are thus consistent with the previous conclusion that the inducer of the multienzyme complex composed of urea carboxylase and allophanate hydrolase is the intermediate compound allophanate.

Induction of Urea-degradative Enzymes during Nitrogen Starvation—Urea, as indicated above, is produced when S. cerevisiae is grown with the amino acid arginine as a nitrogen source. Under these growth conditions arginine is degraded to ornithine and urea by the enzyme arginase. It was found, in our studies of the induction of arginase, that the starvation of the cells for ammonia resulted in an immediate derepression of arginase. It was further shown that this derepression was contingent upon the presence of an arginine pool in the cells; that is, when cells were starved of both arginine and ammonia, no immediate derepression of arginase occurred, although the addition of the nonmetabolizable inducer homomarginine did result in enzyme production under these conditions. The conclusion drawn from these data was that ammonia inhibits the induction of arginase and that under conditions of ammonia starvation, the pool of arginine normally present in cells grown on minimal medium is sufficient to cause induction of arginase. Thus the immediate derepression of enzyme following the onset of nitrogen starvation is, in fact, induction by the normal inducer arginine. Since it was also observed that urea amido-lyase was derepressed following the onset of nitrogen starvation, this phenomenon was examined in further detail.

The derepression of allophanate hydrolase in wild type cells under conditions of nitrogen starvation is shown in Fig. 6A. Exponentially growing cells were filtered and one-half of the culture was resuspended in medium devoid of a nitrogen source; the other half of the culture was respended in the same medium but the nonmetabolizable inducer of the urea degradation system, formamide was added. The inclusion of a culture containing a nonmetabolizable inducer is a necessary control which indicates the level of enzyme synthesis possible in different strains under various conditions. It can be seen that allophanate hydrolase in wild type cultures containing urea and related nitrogen sources. M-25 was grown in minimal medium from which the ammonia had been omitted; urea, formamide, or hydantoic acid was present at a concentration of $1.0 \times 10^{-2}$ M. Growth of the cultures was determined at the indicated times. 

![Fig. 5. Growth of Saccharomyces cerevisiae on urea and related nitrogen sources.](http://www.jbc.org/)

**Table III**

| Inducer            | Amount of allophanate cleaved per min per ml culture (60 Klett units) |
|--------------------|---------------------------------------------------------------------|
|                    | M-25       | M-62       |
| None               | 0.32       | 0.22       |
| Urea               | 2.32       | 0.24       |
| Formamide          | 1.63       | 0.23       |
| Acetamide          | 0.33       | 0.23       |
| Formyl urea        | 0.42       | 0.24       |
| Thiourea           | 0.26       | 0.29       |
| N-Methyl formamide | 0.29       | 0.29       |

**Table IV**

| Inducer            | Amount of allophanate cleaved per min per ml culture |
|--------------------|------------------------------------------------------|
|                    | 60 Klett units | 80 Klett units |
| None               | 0.21          | 0.26          |
| $10^{-3}$ M urea   | 0.27          | 0.36          |
| $10^{-2}$ M hydantoic acid | 0.43   | 0.52          |
| $10^{-2}$ M formamide | 0.26       | 0.24          |

by the normal inducer arginine. Since it was also observed that urea amido-lyase was derepressed following the onset of nitrogen starvation, this phenomenon was examined in further detail. The derepression of allophanate hydrolase in wild type cells under conditions of nitrogen starvation is shown in Fig. 6A. Exponentially growing cells were filtered and one-half of the culture was resuspended in medium devoid of a nitrogen source; the other half of the culture was resuspended in the same medium but the nonmetabolizable inducer of the urea degradation system, formamide was added. The inclusion of a culture containing a nonmetabolizable inducer is a necessary control which indicates the level of enzyme synthesis possible in different strains under various conditions. It can be seen that allophanate hydrolase becomes derepressed following the onset of nitrogen starvation and that the inclusion of formamide in the starvation medium stimulates the production of hydrolase. If this derepression occurs by the same mechanism as that of arginase, then the production of enzyme is due to induction by the urea or allophanate present in the cells. A major source of urea in cells undergoing nitrogen starvation is the large intracellular pool of arginine. The lag preceding the derepression of allophanate hydrolase in the wild type strain, Fig. 6A, might be due to the time necessary to synthesize some arginase and convert the arginine to urea and
Since it has been shown that the inducer of the urea-degradative system is in fact allophanate, it can be predicted that a mutant lacking urea carboxylase, and therefore, unable to produce allophanate from urea, would not be able to produce allophanate hydrolase under conditions of nitrogen starvation. Furthermore, the addition of formamide should not alter the level of enzyme found, since this compound, like urea, must be carboxylated before it is able to serve as an inducer. These predictions are confirmed by the results depicted in Fig. 6C. When the mutant lacking urea carboxylase was deprived of ammonia, either in the presence or absence of formamide, there was no large increase in the amount of allophanate hydrolase found in the cells. The very slight increase seen is probably an increase in the basal level; this increase was observed in all of the experiments and is only visible in this case because the ordinate has been expanded.

**DISCUSSION**

We have shown that in strains containing a nonfunctional urea carboxylase, the synthesis of allophanate hydrolase cannot be induced by urea. In contrast, in wild type strains the level of this enzyme increases 8- to 10-fold upon addition of urea. The same response was observed with two nonmetabolizable analogues of urea. These data are consistent with the suggestion that the inducer of allophanate hydrolase is allophanate. In addition, urea carboxylase activity, in an allophanate hydrolase-defective strain, was observed to be at its fully induced level whether or not urea was added to the culture. This observation may be accounted for by suggesting that allophanate is also the inducer of urea carboxylase and that in the hydrolase-deficient organism allophanate, which cannot be degraded, accumulates as a result of the metabolism of arginine. This conclusion can be questioned, however, if the reaction catalyzed by urea carboxylase is reversible. Under this condition it would not be possible to distinguish whether urea or allophanate is the legitimate inducer. While the possibility of urea being the inducer of urea carboxylase is considered unlikely (the carboxylation reaction is only slightly reversible) the only way to establish with certainty that allophanate is the inducer of urea carboxylase is to monitor the affect of adding urea, to wild type and carboxylase-defective strains, on the amount of immunochemically detectable urea carboxylase cross-reacting material. The suggestion that allophanate acts as the inducer of both urea carboxylase and allophanate hydrolase is reasonable since preliminary evidence indicates that the structural genes responsible for the synthesis of these two enzymes are contiguous. The present situation is similar to that observed for induction of the first two enzymes responsible for tryptophan degradation in *Pseudomonas* (12) and induction of the histidine utilization enzymes in *Aerobacter* (13). Palleroni and Stanier (12) demonstrated that the inducer of the first two enzymes of tryptophan degradation was kynurenine, the product of the second enzyme in the pathway, and Schlegel et al. (18) showed that the enzymes of the histidine-degradative pathway are induced by urocanic acid the product of the first enzyme in the pathway. In these cases, however, the first activity of each pathway is irreversible, so that the conclusion is unambiguous.

In the previous paper, data were presented showing that the urea-degradative enzymes were apparently derepressed during growth of this organism under conditions of nitrogen starvation. Here we have looked at this question more thoroughly and have

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**FIG. 6.** Production of allophanate hydrolase in wild type and mutant strains following the onset of nitrogen starvation. The indicated strain was grown to a density of 86 Klett units in minimal medium containing ammonia as the sole nitrogen source; the culture was split and filtered to begin starvation. The cells from one half of the culture were resuspended in minimal medium containing glucose but no nitrogen source, while the cells from the second half of the culture were resuspended in the same medium containing 1.0 X 10^-3 M formamide. Samples of the cultures were removed and allophanate hydrolase activity was determined as described under "Materials and Methods." The strains used were the wild type, M-25 (A), the mutant lacking arginase activity, M-58 (B), and the mutant lacking urea carboxylase activity, M-62 (C).

then to allophanate. It should be noted that this lag was much shorter when the inducer formamide was present in the starvation medium. The production of urea from arginine can be eliminated by the use of a mutant strain lacking arginase activity. As can be seen in the experiment in Fig. 6B, nitrogen starvation of such a mutant results in no immediate derepression of allophanate hydrolase. In the control culture which received formamide, this enzyme could be induced indicating that the cells still have the capacity to synthesize this protein when provided with inducer.
demonstrated that the apparent derepression of the urea-degradative system is contingent upon the presence of the inducer, allophanate. During conditions of nitrogen starvation the intracellular pool of arginine is sufficient to effect the induction of arginase. The production of arginase presumably allows the degradation of arginine to urea and subsequently to allophanate. Allophanate in turn brings about the induction of the urea-degradative system. The apparent derepression is, therefore, in fact an example of internal induction.

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