Reversible Inactivation of Phenylalanine Hydroxylase by Catecholamines in Cultured Hepatoma Cells*

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MICHAEL R. MILLER$ AND ROSS SHIMAN

From the Department of Biological Chemistry, The Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, Pennsylvania 17033

Phenylalanine hydroxylase in Reuber H4 hepatoma cell cultures can be rapidly inactivated by the addition of epinephrine, norepinephrine, dopamine, or 3,4-dihydroxyphenylalanine, in order of decreasing effectiveness, to the culture medium. The enzyme was 50% inactivated in 1 hour by 25 μM (R)-epinephrine or 45 μM (R)-norepinephrine in the medium. High concentrations of epinephrine caused a 70% inactivation in 15 min. Phenylalanine hydroxylase appears to be reversibly inactivated by epinephrine within the cells; since washing the compound off the cell culture resulted in a rapid recovery of enzyme activity (40% in 1 hour), cycloheximide had little effect on the initial rate of recovery of enzyme activity and the same amount of phenylalanine hydroxylase antigen per cell was isolated from treated and normal cultures. Both (S)- and (R)-epinephrine inactivated the enzyme, and 0.1 mM desmethylimipramine, an inhibitor of amine transport, significantly decreased the effect of epinephrine on the hydroxylase activity. The possibility, suggested by the above results, that epinephrine might be directly inactivating phenylalanine hydroxylase within the cells was supported by the finding that purified rat liver phenylalanine hydroxylase would be 50% inactivated by 1.5 μM epinephrine in 10 min.

In studying the regulation of phenylalanine hydroxylase (L-phenylalanine tetrahydropteridine:oxygen oxidoreductase (4-hydroxylating), EC 1.14.16.1) in the Reuber H4 (1) rat hepatoma cell line, we found that catecholamines could rapidly and efficiently reduce this enzyme's activity in growing cell cultures. Burkard et al. (2) had reported that catecholamines inhibited phenylalanine hydroxylase in a cell-free system, and Kaufman (3) has indicated that homogeneous phenylalanine hydroxylase could be inhibited by norepinephrine. Bublitz (4) also reported, with the use of a partially purified phenylalanine hydroxylase, that a variety of catechols could, apparently irreversibly, inactivate the enzyme in a process that could be distinguished from the kinetic inhibition. With the exception of a report showing that α-methyl-3,4-dihydroxyphenylalanine could not inactivate rat liver phenylalanine hydroxylase, to some extent (5) in vivo, there has been little evidence that either the inhibition or inactivation by catecholamines could be observed in situ.

The ability of catecholamines to regulate phenylalanine hydroxylase activity could be of physiological importance. The enzyme activity is found mainly in mammalian liver and kidney tissue, and all significant endogenous tyrosine synthesis in mammals is catalyzed by this enzyme (3). Phenylalanine hydroxylase has been well characterized in the Reuber H4 hepatoma cell line, and effects of cell-cell interactions (6, 7), glucocorticoid (7-9), and p-chlorophenylalanine (8, 10) on the enzyme have been studied. The present investigations have been carried out in the same cell line; and this communication characterizes the inactivation of phenylalanine hydroxylase by catecholamines in H4 cells.

MATERIALS AND METHODS

Chemicals—(S)- and (R)-epinephrine was purchased from K&K Laboratories and Sigma Chemical Co. Crystalline catalase was purchased from Calbiochem. All radioactive compounds were purchased from Amersham/Searle. 6-Methyldihydropterin was synthesized according to Storm et al. (11). All other compounds were purchased from Sigma Chemical Company.

Cell Culture—The Reuber hepatoma cell line H4 (1) was used in all cell culture studies. The cells were grown in monolayer culture with a modification (12) of Medium S-77 containing 2 times glutamine and 10% fetal calf serum, but containing no antibiotics. Detailed cell culture conditions have been previously described (8). Cells were found to be free of mycoplasma by the method of Schneider et al. (13).

On the day of use, catechols and p-chlorophenylalanine were dissolved in a small volume of 0.2 N HCl, diluted into medium at the appropriate concentration, and the pH was immediately adjusted to 7.4, when necessary. (The addition of a small volume of 0.2 N HCl to medium followed by rapid neutralization was determined not to affect H4 cell growth or the activity of phenylalanine hydroxylase, lactate dehydrogenase, or tyrosine aminotransferase.) Medium containing the experimental compounds was resterilized by Millipore filtration.

Preparation of H4 Cell Extract—Detailed methods for the preparation of H4 cell extract have been described (8). Protein in the extracts was determined by the method of Lowry et al. (14) with bovine serum albumin as the standard.
Catecholamine Inactivation of Phenylalanine Hydroxylase

Enzyme Assays—Lactate dehydrogenase was measured by recording the pyruvate-dependent oxidation of NADH at 340 nm (15). Specific activity was expressed as ΔA,454/min/mg of soluble protein. Tyrosine aminotransferase was assayed according to Granner and Tomkins (16) by measuring the change in absorbance due to p-hydroxyphenylpyruvate production at 331 nm. Specific activity was expressed as ΔA,220/min/mg of soluble protein.

Phenylalanine hydroxylase activity in H4 cell extracts was assayed by measuring the formation of [3H]tyrosine from [1-14C]phenylalanine by our published procedure (8). This phenylalanine hydroxylase radioactive assay contained 82 mM K2HPO4, pH 6.8, 0.9 mM L-tyrosine, 64 mM L-phenylalanine, 50 mM 6-methyltetrahydropterin, 2.1 mM dithiothreitol, 16 μg of catalase, L-[1-14C]phenylalanine (2 to 3 × 104 cpm), cell extract, and water in a final volume of 0.25 ml (8). Specific activity is given as nanomoles of tyrosine formed/min/mg of soluble protein. It should be noted that the concentration of phenylalanine in this phenylalanine hydroxylase assay has been increased from 0.2 mM (8) to 0.4 mM.

Phenylalanine Hydroxylase Antibody Studies and Purification—Antiserum prepared against purified rat liver phenylalanine hydroxylase was used to determine the amount of incorporation of radioactivity labeled amino acids into H4 cell phenylalanine hydroxylase. The phenylalanine hydroxylase antiserum was the generous gift of Dr. S. Kaufman, National Institutes of Health. The antiserum has been characterized against rat liver (17) and H4 cell phenylalanine hydroxylase (7). Phenylalanine hydroxylase antigen was recovered from cell extracts as described (7).

Phenylalanine hydroxylase was purified from rat liver through the DEAE-step of Kaufman’s procedure (18). Electrophoresis on polyacrylamide gel in the presence of sodium dodecyl sulfate and staining with Coomassie blue (19) indicated the preparation was 40 to 50% homogeneous at this point.

Scintillation counting procedures have been described (8). Internal standards were used to determine counting efficiencies. Quench corrections were made where necessary.

Results

Effect of Catecholamines on Phenylalanine Hydroxylase Activity in Reuber H4 Hepatoma Cells—H4 cell cultures were incubated in medium containing p-chlorophenylalanine, 3,4-dihydroxyphenylalanine, dopamine, norepinephrine, or epinephrine and 6 hours later assayed for phenylalanine hydroxylase, lactate dehydrogenase, and tyrosine aminotransferase activities. Table I shows that all the catechols decreased the phenylalanine hydroxylase activity and all to a greater extent than did p-chlorophenylalanine. Little or no effect could be seen on lactate dehydrogenase, soluble protein, or, with the exception of dopamine, tyrosine aminotransferase activity. Similar results were obtained when cultures were treated with the same compounds for 12 hours.

Mixing experiments were performed in which extract from control cultures was assayed alone or in the presence of an equal volume of extract from treated cultures. In the experiment in Table I, the combined extracts were preincubated 30 min at 0°, and then assayed. An additive recovery of phenylalanine hydroxylase activity (within 10%) was observed in all cases (Table I). Identical results were obtained when control and treated cell extracts were combined and assayed without prior incubation at 0°. Thus, there was neither a phenylalanine hydroxylase inhibitor in the treated cell extracts nor could the control extracts relieve the inhibition.

Effect of Epinephrine Concentration on Phenylalanine Hydroylase in H4 Cells—Because epinephrine appeared to be the most potent inactivator of phenylalanine hydroxylase activity (Table I), the effect of this catecholamine was further studied. Replicate cultures of hepatoma cells were fed normal medium or normal medium containing different amounts of epinephrine and assayed 1 hour later. Fig. 1 shows that 25 μM epinephrine caused a 50% loss of enzyme activity in 1 hour.

TABLE I

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hydroxylase activity</th>
<th>Soluble protein per culture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDH*</td>
<td>TAT*</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (control)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mM p-Chlorophenylalanine</td>
<td>3.56</td>
<td>2.5</td>
</tr>
<tr>
<td>1 mM Dopamine</td>
<td>2.37</td>
<td>2.7</td>
</tr>
<tr>
<td>1 mM Dopamine + 1 mM PBS-CMF°</td>
<td>0.76</td>
<td>3.0</td>
</tr>
<tr>
<td>1 mM Norepinephrine</td>
<td>0.52</td>
<td>2.9</td>
</tr>
<tr>
<td>1 mM Epinephrine</td>
<td>0.32</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Extracts mixed

<table>
<thead>
<tr>
<th>Extracts mixed</th>
<th>Hydroxylase activity</th>
<th>Theoretical</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control + PBS-CMF°</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Control + p-Chlorophenylalanine</td>
<td>175</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>Control + Dopamine</td>
<td>150</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>Control + Dopamine</td>
<td>116</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>Control + norepinephrine</td>
<td>111</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Control + epinephrine</td>
<td>10</td>
<td>101</td>
<td></td>
</tr>
</tbody>
</table>

*LDH, lactate dehydrogenase.
†TAT, tyrosine aminotransferase.
‡Dopa, 3,4-dihydroxyphenylalanine.
§PBS-CMF, calcium-magnesium-free phosphate-buffered saline.

Neither lactate dehydrogenase nor tyrosine aminotransferase (Fig. 1) nor total cellular protein (not shown) were significantly affected by even the highest epinephrine concentration.

The presence or absence of serum in the medium had no obvious effect on the epinephrine-dependent loss of phenylalanine hydroxylase activity. It might be mentioned that cultures maintained for 24 hours in normal medium containing 0.25 mM (R) epinephrine showed no toxic effects. (This is in distinction to the recent report of Haggerty et al. (20) that cells starved for serum for 72 hours showed toxic effects from 10−4 M epinephrine.)

(R)-Norepinephrine was somewhat less effective than (R)-epinephrine in decreasing the phenylalanine hydroxylase ac-
The (S) isomer of epinephrine was also capable of reducing phenylalanine hydroxylase activity relatively rapidly (Fig. 3). The initial recovery of enzymatic activity under these conditions was not appreciably affected by the presence of 10^{-5} M cycloheximide. (This amount of cycloheximide will inhibit amino acid incorporation 95% in 1 hour in these cells (10).) Identical results were obtained with (R)-norepinephrine (and other catechols) in vitro, although the concentrations required were somewhat greater than we had previously observed. For instance, Gielen and Nebert (21) found (S)-norepinephrine slightly more effective than (R)-norepinephrine in elevating aryl hydrocarbon hydroxylase activity in liver cells in culture.

**Time Course of Epinephrine-mediated Loss of Phenylalanine Hydroxylase Activity**—Fig. 2 shows the time course of loss of phenylalanine hydroxylase activity after the addition of high levels of epinephrine to the culture medium. Within 15 min the hydroxylase activity dropped to 30% of control; then, it slowly decreased to approximately 10% of control in the next 3 hours. Lactate dehydrogenase specific activity after epinephrine addition to cultured hepatoma cells. Specific activity represents nanomoles of tyrosine formed/min/mg of soluble protein; tyrosine aminotransferase specific activity is ΔA_{412}/min/mg of soluble protein; lactate dehydrogenase specific activity is ΔA_{340}/min/mg of soluble protein.

**Antibody Assay for Phenylalanine Hydroxylase in Cultured Cells Treated with Epinephrine**—The immediate recovery of phenylalanine hydroxylase activity following removal of epinephrine, even in the presence of cycloheximide (Fig. 3) implied that the amount of phenylalanine hydroxylase protein in the cells was not affected by epinephrine. To directly establish this, antibody to purified rat liver phenylalanine hydroxylase was employed to isolate the enzyme from control and treated cell extracts; and the amounts of antigen present were compared (Table II). To ensure uniform labeling of cell proteins, cells were plated into culture flasks at one-fifth confluent density and grown to confluency in normal medium containing L-[3H]leucine, with daily changes of the medium. At the end of this time, one culture received radioactive medium alone (control), while the other culture received radioactive medium containing epinephrine; after 24 hours of incubation, cell extract was prepared and phenylalanine hydroxylase antigen isolated. Table II shows the results of one such experiment. In this case treatment with epinephrine decreased phenylalanine hydroxylase specific activity to 30% of control, but did not decrease the amount of labeled phenylalanine hydroxylase antigen below that found in the control culture. The results of Table II and Fig. 3 indicate that epinephrine reversibly inactivates phenylalanine hydroxylase and has no effect on the amount of enzyme protein in the cells.

**Inactivation of Purified Phenylalanine Hydroxylase by Epinephrine**—The preceding experiments suggested that epinephrine could be acting directly on phenylalanine hydroxylase, in the H4 cells, to inactivate the enzyme. This possibility was supported by the report of Ruhllitz (4) that partially purified phenylalanine hydroxylase could be inactivated by norepinephrine (and other catechols) in vitro, although the concentrations required were somewhat greater than we had previously observed. For instance, Gielen and Nebert (21) found (S)-norepinephrine slightly more effective than (R)-norepinephrine in elevating aryl hydrocarbon hydroxylase activity in liver cells in culture.
found necessary. This problem has been reinvestigated by means of relatively highly purified phenylalanine hydroxylase.

In the experiment shown in Fig. 4, phenylalanine hydroxylase was preincubated prior to the addition of substrates for 10 min at 25° with different concentrations of (R)-epinephrine. Concentrations of epinephrine as low as 0.1 μM produced a detectable effect and 1.5 μM caused a 50% decrease in the measured initial velocity. The inactivation is a time-dependent process, and in the absence of any preincubation even 50 μM epinephrine had no effect on the initial velocity. (S)- and (R)-epinephrine were equally effective inactivators of the enzyme. L-3,4-dihydroxyphenylalanine, dopamine, and norepinephrine could also inactivate the purified phenylalanine hydroxylase (not shown).

Effect of Inhibitors of Epinephrine Action—Experiments with agents that are known to block the effects of epinephrine in tissues and cells (22) were also consistent with the possibility of epinephrine directly inactivating phenylalanine hydroxylase in situ. Phentolamine, propranolol, and desmethylimipramine (α receptor, β receptor, and catecholamine transport inhibitors, respectively) were added at different concentrations to a series of replicate cultures in the presence and absence of 0.1 mM (R)-epinephrine. The epinephrine was added 10 min after the addition of the inhibitors and 90 min later all the cultures were harvested and assayed for phenylalanine hydroxylase activity. Cultures with epinephrine alone, or epinephrine plus 1.0 mM phentolamine, 0.1 mM propranolol, or 0.1 mM desmethylimipramine had specific activities of 21, 38, 40, and 68% of control culture activities. These were the highest concentrations of these compounds tested. Higher concentrations of propranolol or desmethylimipramine were toxic.

Since epinephrine effects mediated by β receptors apparently occur through stimulation of cAMP formation (23) and dibutyryl cAMP causes a slight increase in the hydroxylase activity (7, 24) in the H4 cells, β receptor interaction that causes an increase in cAMP does not seem a likely route for the

![Fig. 3. Recovery of phenylalanine hydroxylase activity in hepatoma cells following removal of epinephrine. Replicate confluent cell cultures were fed normal medium or normal medium containing 0.5 mM epinephrine. One hour later (“0 hour”) cultures in epinephrine-containing medium were fed normal medium (○), normal medium containing 10^-5 M cycloheximide (Δ), or normal medium containing 0.5 mM epinephrine (■). Cultures in normal medium were fed either normal medium (control) or normal medium containing 10^-5 M cycloheximide (■). At the indicated times, cells were harvested and assayed for phenylalanine hydroxylase; the hydroxylase specific activity is expressed as a percentage of hydroxylase specific activity in control cultures harvested at the same time.

**TABLE II**

<table>
<thead>
<tr>
<th>Description</th>
<th>Control</th>
<th>Epinephrine 0.25 mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 3H cpm/mg of total protein</td>
<td>1.82 x 10^8</td>
<td>1.93 x 10^8</td>
</tr>
<tr>
<td>2. 14C-internal standard (relative recovery)</td>
<td>100%</td>
<td>96%</td>
</tr>
<tr>
<td>3. 3H-antigen specific activity (corrected counts per min/mg of protein)</td>
<td>678</td>
<td>652</td>
</tr>
<tr>
<td>4. 3H-antigen specific activity (% of control)</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>5. Enzymatic specific activity (% of control)</td>
<td>100</td>
<td>30</td>
</tr>
</tbody>
</table>

![Fig. 4. Inactivation of purified phenylalanine hydroxylase by (R)-epinephrine. In this experiment, epinephrine was added at one of the indicated concentrations to 0.85 ml of a mixture of phosphate buffer and catalase (see below), followed immediately by purified phenylalanine hydroxylase. The mixture was incubated in the dark for 10 min, at which time L-phenylalanine was added. After 3 min of further incubation, the enzyme reaction was initiated by the addition of dithiothreitol and 6-methyltetrahydropterin and the initial velocity determined spectrophotometrically (8). “Hydroxylase activity” represents nanomoles of tyrosine formed/min for a series of identical aliquots of purified phenylalanine hydroxylase. The components of the spectrophotometric assay (8) are 80 mM potassium phosphate, 64 μg of crystalline catalase, 1 mM L-phenylalanine, 5 mM dithiothreitol, 90 μM 6-methyltetrahydropterin and phenylalanine hydroxylase, all at pH 6.8 and in a final volume of 1.00 ml. The reaction is monitored at 275 nm. All above incubations are at 25°. The 6-methyltetrahydropterin and (R)-epinephrine solutions were freshly made up in 0.005 N HCl and 0.01 N HCl, respectively; both solutions were kept at 0°, and the epinephrine always in the dark.
epinephrine-dependent inactivation. Desmethylimpromipramine, which can block uptake of catecholamines into the cell interior (25, 26) had the most significant effect of the inhibitors tested in blocking the epinephrine-induced inactivation. This observation does support the idea that the catecholamines could go directly into the cell interior and there inactivate phenylalanine hydroxylase. However, it must be recognized that these three above compounds are sufficiently toxic to the cells that effects of the α and β receptor inhibitors could have been masked.

**DISCUSSION**

A number of lines of evidence indicate that epinephrine could decrease phenylalanine hydroxylase activity in H4 cells by directly inactivating this enzyme. The rate of loss of hydroxylase activity following the addition of epinephrine to the cultured cells is rapid and nearly complete in 15 min (Fig. 1); after 24 hours in the presence of epinephrine no decrease in the amount of phenylalanine hydroxylase antigen present in the cells could be seen (Table II) and recovery of hydroxylase activity following epinephrine removal was not dependent on protein synthesis (Fig. 3). (This last observation is the first indication that catechols do not irreversibly inactivate phenylalanine hydroxylase.) In addition, we found that desmethylimpromipramine (an inhibitor of amine transport) had a significant effect in preventing the epinephrine-dependent reduction of the hydroxylase activity; and that (S)-epinephrine was at least as effective as (R)-epinephrine in decreasing phenylalanine hydroxylase activity in the cultured cells. It was also shown that the activity of purified rat liver phenylalanine hydroxylase could be drastically reduced by a 10-min exposure to low levels of epinephrine (Fig. 4). Taken together these observations suggest, although they do not prove, that the epinephrine-mediated reduction of phenylalanine hydroxylase activity in H4 cells is due to uptake of the compound into the cells followed by direct inactivation of the hydroxylase.

Bublitz (4) has shown that catechols inhibit purified rat liver phenylalanine hydroxylase through two separate mechanisms, (a) a competitive inhibition of the hydroxylase with reduced pyridoxal cofactor, and (b) an inactivation of this enzyme. In H4 cells we have presumably been studying only the latter mechanism (inactivation of the hydroxylase) as shown by the mixing experiments in Table I. Our studies concerning the effect of epinephrine on purified rat liver phenylalanine hydroxylase activity (Fig. 4) have explicitly dealt with the inactivation of this enzyme, rather than the competitive inhibition. Tretting purified phenylalanine hydroxylase in the absence of substrates resulted in 50% loss of activity by 1.5 μM epinephrine (Fig. 4), and norepinephrine was even more effective in reducing the hydroxylase activity. These values are a great deal lower than the 55% loss (inactivation) of phenylalanine hydroxylase activity by 75 μM norepinephrine reported by Bublitz (4). The origin of the discrepancy almost certainly lies in the fact that he (4) exposed the hydroxylase to norepinephrine in the presence of 3 mM phenylalanine. Both phenylalanine and also 6-methyltetrahydropterin will interfere with the inactivation by epinephrine; and the studies in Fig. 4 were performed by mixing phenylalanine hydroxylase with epinephrine in the absence of substrates.

It is possible to describe at least two simple mechanisms consistent with all the data through which epinephrine might inactivate phenylalanine hydroxylase in the H4 cells. (a) The catecholamine could bind tightly to the enzyme, in or near an active site, rendering the hydroxylase inactive; or (b) it could dissociate the hydroxylase into inactive subunits. Both mechanisms would by their nature be slowly reversible. The particular chemical species accomplishing this could be an α-quinate, as has been proposed (4) by Bublitz in his studies, or the catecholamine itself. (The matter is currently under investigation.) Despite the structural similarities of the catecholamines and p-chlorophenylalanine, which also can inactivate phenylalanine hydroxylase in the H4 cells (8, 10) and in vivo (27), actions of these two compounds on phenylalanine hydroxylase differ in nearly every detail (8, 10). The compounds almost certainly work through different mechanisms.

This communication is the first to directly show that catecholamines can inactivate phenylalanine hydroxylase in situ; and these findings almost certainly explain the effects of the unnatural catechols α-methyl-3,4-dihydroxyphenylalanine (5) and esculin (6,7-dihydroxy coumarin 6-glucoside) (28) in vivo on liver phenylalanine hydroxylase activity. It is difficult to assess the physiological importance of the inactivation by catecholamines. Even though the plasma levels of epinephrine are probably quite low, there have been many reports of epinephrine effects at concentrations equal to or greater than those required on the present case, in inducing aryl hydrocarbon hydroxylase in cultured liver cells (21), accelerating sugar transport in avian erythrocytes (26), activating adenylate cyclase in turkey and frog erythrocytes (29, 30), stimulating cAMP formation in pigeon erythrocytes (31) and in cultured WI-38 fibroblasts (32), and stimulating cAMP accumulation and lipolysis in rat epididymal fat pad (33). Furthermore, there is reason to believe that the effect of epinephrine in the cells might be able to occur at lower concentrations than we apparently found: the initial rate of recovery of enzyme activity once the epinephrine is removed is so rapid (Fig. 3) that some enzyme is almost certainly reactivated in the 20 to 25 min required to wash, harvest, and lyse several cultures; and the purified phenylalanine hydroxylase can be detectably inactivated with 10⁻⁷ M epinephrine, which may be within the physiological range. There are also conditions, such as Parkinson's disease, where individuals may be given enormous amounts of L-3,4-dihydroxyphenylalanine for extended periods of time (34); and it seems possible that this treatment could, among its other effects, reduce the activity of phenylalanine hydroxylase and alter the normal metabolism of phenylalanine or the availability of tyrosine.

**REFERENCES**


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3676 Catecholamine Inactivation of Phenylalanine Hydroxylase

Reversible inactivation of phenylalanine hydroxylase by catecholamines in cultured hepatoma cells.
M R Miller and R Shiman


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