Effects of Malnutrition on Rat Myocardial
β-Adrenergic and Muscarinic Receptors

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Malnutrition, as well as malignancy, induces alterations in heart metabolism and performance. Previous studies have implicated adrenergic mechanisms as the cause. The present study was undertaken to investigate if the adenylate cyclase system in the rat heart was affected by malnutrition. Three different animal groups with malnutrition were compared with a control group: rats with acute starvation for 14–96 hours, rats with protein-calorie malnutrition for 2 weeks, and rats with tumors. Stimulation by β-adrenergic receptors and inhibition by muscarinic receptors of adenylate cyclase activity were not altered by malnutrition. However, conditions used for in vitro adenylate cyclase determinations were, of necessity, not physiological. Neither did the number of β-adrenergic and muscarinic receptors change. When competition-binding experiments were performed, differences comprising agonist affinity and affinity state distribution were noted among the groups. The myocardial β-adrenergic receptors formed a reduced number of high-affinity sites in all groups as compared with the control rats. All high-affinity sites displayed a more than 10-fold increase in affinity toward isoproterenol and an impaired sensitivity to guanine nucleotides except in heart membranes derived from rats starved less than 48 hours. While the protein-calorie restricted and the tumor-bearing rats had myocardial β-adrenergic receptors that were unresponsive to guanine nucleotides, after 48 hours of starvation the rats exhibited an attenuated guanine-nucleotide-induced affinity shift. No changes associated with malnutrition in myocardial membrane levels of the stimulatory guanine-nucleotide-binding protein were detected by cholera-toxin-induced ADP-ribosylation. In competition binding between quinuclidinyl benzilate and carbachol, myocardial muscarinic receptors derived from malnourished rats exhibited a three-site affinity distribution whereas control rats displayed a two-site affinity distribution. The observations on myocardial β-adrenergic and muscarinic receptors in malnourished rats are consistent with alterations in receptor and regulatory guanine-nucleotide-binding protein interaction. Our results point to the possibility of regulating cell functions by modifying coupling mechanisms. In addition, β-adrenergic receptors displayed a considerably increased affinity towards isoproterenol, which fact may contribute to the earlier findings of β-adrenergic hypersensitivity in malnutrition. (Circulation Research 1989;64:949–956)

Cancer patients have elevated resting energy expenditure,1–3 but the mechanisms behind such increased metabolic rates are not fully understood. By using the isolated working rat heart model, we have recently demonstrated an elevated oxygen consumption in hearts from tumor-bearing animals while a diminished oxygen consumption was found in malnourished animals.4 In addition, hearts derived from either malnourished or tumor-bearing rats have been reported to exhibit an increased sensitivity toward β-adrenergic stimulation as judged by a norepinephrine-stimulated heart rate, contractility, and peak systolic pressure.4 In experiments reported by others, acute starvation seemed to induce a decreased norepinephrine turnover with an unchanged tissue concentration of catecholamines in rat hearts,5 whereas chronic protein deprivation may raise the myocardial norepinephrine concentration.4 Adrenergic hypersensitivity does not seem to be confined to heart tissue but has also been demonstrated in adipocytes.6–9 In addition, many cancer patients have elevated plasma levels of catecholamines in conjunction with augmented tissue sensitivity toward β-adrenergic
stimulation. Thus, evidence suggests that undernutrition is associated with an altered adrenergic state.

The aim of the present study was therefore to investigate whether increased responsiveness to catecholamines in malnutrition can be attributed to adaptive phenomena at the receptor level.

Materials and Methods

[1H]Quinuclidinyl benzilate (QNB), [32P]ATP, [3H]cyclic AMP (cAMP), and [3H]Iodocyanopindolol (ICYP) were obtained from the New England Nuclear Corp, Boston, Massachusetts. All other chemicals were of analytical grade and obtained from the Sigma Chemical Co, St. Louis, Missouri.

Male Sprague-Dawley rats weighing 80–90 g were purchased from Anticimex, Stockholm, Sweden. Three groups of rats suffering from manifest malnutrition served as study animals as compared with freely fed control animals with normal growth rates.

Freely eating, tumor-bearing rats suffering from mild anorexia but with profound alterations in body composition due to the malignant tumor growth were used in one study group. The tumor-bearing rats were implanted subcutaneously with a methylcholanthrene-induced sarcoma in the flanks, using a trocar. The tumor did not penetrate the abdominal cavity nor impair movement before the animals were killed 3 weeks after implantation. The tumor does not metastasize.

The other two study groups, with overt malnutrition, were composed of rats on a protein-free diet for 2 weeks and of rats subjected to acute starvation for 24–36 hours before being killed. The rats fed the protein-free diet suffered from severe protein-calorie malnutrition (PCM) leading to an almost complete cessation of growth. The composition of the protein-free diet has been given elsewhere. All rats had free access to tap-water and were kept in a room with constant temperature and humidity.

Membrane Preparation

Rats were anesthetized by intraperitoneal injection of pentobarbital (Nembutal, 60 mg/kg/body wt), and the heart was quickly dissected out and washed free of blood in ice-cold homogenizing buffer containing 20 mM Tris-HCl (pH 7.6), 250 mM sucrose, 1 mM MgCl2, and 1 mM dithiothreitol. All steps in membrane preparation were performed at 4°C. The heart was then minced and homogenized in 7–10 volumes of buffer with a Polytron mechanical homogenizer (Kinematica GmbH, Lucerne, Switzerland) with three 10-second bursts at 1-minute intervals. The homogenate was filtered through two layers of cheese cloth and centrifuged at 8,000g for 10 minutes. The supernatant was further spun at 37,000g for 30 minutes. The pelleted membranes were then washed once with 0.6 M KCl in homogenizing buffer followed by two washes with pure homogenizing buffer to remove contractile proteins. The final pellet was dispersed to give a protein concentration of about 5 mg/ml in phosphate-buffered isotonic saline (pH 7.4).

Radioligand Binding Studies

The tracers used were [1H]QNB and [125I]ICYP for muscarinic (agonist, carbachol) and β-adrenergic (agonist, isoproterenol) receptors, respectively. Binding assays were carried out in phosphate-buffered saline (pH 7.4) composed of 137 mM NaCl, 4.2 mM KCl, 20 mM phosphate-buffer, 1.5 mM CaCl2, and 1.0 mM MgCl2. An aliquot of the membrane preparation was incubated for 1 hour in a total volume of 0.2 ml at 26°C with either 0.4 nM tritiated QNB (muscarinic binding assay) or 0.05 nM iodinated CYP (β-adrenergic binding assay) and indicated concentrations of carbachol or isoproterenol, respectively. The reaction was terminated by dilution with 5 ml ice-cold phosphate-buffered saline. The samples were then immediately poured over a GF/F 25 mm Whatman glass filter (Whatman LabSales Inc, Hillsboro, Oregon) under reduced pressure, followed by a wash with 15 ml of the same buffer. Filters were placed in 20-ml scintillation vials with 1 ml of 1 M HCl and 10 ml of scintillation fluid (Aquasol, New England Nuclear, Boston, Massachusetts) and were counted in a Packard liquid scintillation spectrometer (Packard Instrument Co, Inc, Downers Grove, Illinois).

Saturation-binding isotherms for muscarinic and β-adrenergic receptors were obtained by incubating membranes with varying concentrations of tritiated QNB (0.1–3.0 nM) or ICYP (10–300 pM), respectively, in the above-described buffer for 1 hour. Nonspecific binding was determined by a 100-fold excess of either scopolamine or alprenolol and never exceeded 5%.

Data Analysis

Statistical comparisons between animal groups were done by analysis of variance. Variances were tested statistically for equality by an F test. Differences between specific groups were tested by Student’s t test. Saturation and competition binding curves were analyzed by computer-assisted techniques using both linear and nonlinear regression analysis. To determine if the data were fit significantly (p<0.001) better by the multisite model, the residual sums of squares of the respective fits were compared using an F test. Finally, binding parameters were corrected according to Cheng and Prusoff. Variations are given as mean±SEM.

Relative Changes in the Stimulatory Guanine-Nucleotide-Binding Protein

Cholera-toxin–induced ADP-ribosylation of membranes was performed as described elsewhere. Briefly, cholera toxin was preincubated for 20 minutes at 30°C in 25 mM dithiothreitol in 50 mM Tris-HCl, pH 8.0; 100 μg/ml of the toxin was then incubated with 100 μg membrane protein in a buffer having the following composition: 10 μM
Table 1. Effects of Malnutrition on [125I]ICYP and [3H]QNB Binding to Rat Myocardial Membranes Obtained From One Control and Three Study Groups

<table>
<thead>
<tr>
<th>Rat group</th>
<th>Bmax (fmol/mg protein)</th>
<th>Kd (pM)</th>
<th>Bmax (fmol/mg protein)</th>
<th>Kd (pM)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>122 ± 12</td>
<td>64 ± 9</td>
<td>730 ± 40</td>
<td>0.36 ± 0.05</td>
<td>10</td>
</tr>
<tr>
<td>Starved</td>
<td>127 ± 11</td>
<td>66 ± 13</td>
<td>770 ± 50</td>
<td>0.26 ± 0.07</td>
<td>6</td>
</tr>
<tr>
<td>PCM</td>
<td>139 ± 32</td>
<td>59 ± 12</td>
<td>750 ± 60</td>
<td>0.27 ± 0.06</td>
<td>5</td>
</tr>
<tr>
<td>Tumor-bearing</td>
<td>118 ± 17</td>
<td>61 ± 8</td>
<td>690 ± 70</td>
<td>0.31 ± 0.06</td>
<td>7</td>
</tr>
</tbody>
</table>

Values given are means ± SEM. All differences are nonsignificant (p > 0.05).

ICYP, iodocyanopindolol; QNB, quinuclidinyl benzilate.

[125I]NAD, 2.5 mM MgCl2, 1 mM ATP, 10 mM thymidin, 1 mM EDTA, 1 mM dithiothreitol, and 50 mM Tris-HCl, pH 8.0. The reaction was terminated after 60 minutes by fivefold dilution with sample buffer, protein was precipitated with 20% trichloroacetic acid, and the pellet was washed with acetone. The pellet was then dissolved in sample buffer and applied to an 11% sodium dodecyl sulfate–polyacrylamid gel and electrophoresed. Autoradiography followed by densitometry was used to quantitate the incorporated radiolabel.

Assay of Adenylate Cyclase

Adenylate cyclase was determined according to Hanoune et al.15 Briefly, the assay medium contained a final volume of 60 μl 0.5 mM [32P]ATP (1 million cpm), 1 mM cAMP, 7 mM MgCl2, 1 mM theophylline, 30 mM Tris-HCl (pH 7.6), and an ATP-regenerating system consisting of 1 mM phosphocreatine and 1 mg/ml creatine kinase. Incubation was initiated by the addition of the membrane fraction (20 μl = 87–106 μg protein) and was terminated, after 15 minutes in a shaking water bath at 30°C, by addition of 200 μl 0.5 M HCl followed by immediate boiling for 6 minutes. The pH of the assay mixture was then adjusted to 7.5 with 200 μl of 1.5 M imidazole. The suspension was finally applied to an alumina column. cAMP was eluted with 3 ml of 10 mM imidazole-HCl (pH 7.5) and counted after adding 10 ml scintillation fluid. The yield was calculated by the previous addition of tritiated cAMP. Determinations were usually performed in duplicate or triplicate. Blank values obtained constituted <19% of basal values.

Protein Determinations

The protein concentration was assayed according to Lowry et al.16

Results

Effect of Malnutrition on Rat Weight

All animals had the same initial body weight when allocated to the study groups. Carcass weight (body weight minus tumor weight) was 203 ± 8 g in the tumor-bearing group, 161 ± 7 g in the 96-hour starved rats, and 93 ± 2 g in the PCM group as compared with 248 ± 6 g in the control animals.

Tumor wet weight was 41 ± 5 g (17% of body weight). In a separate experiment evaluating the time course of the effects induced by starvation, rats were starved for 0, 24, 48, and 96 hours leading to relative body weights of 100 ± 3%, 95 ± 4%, 93 ± 6% and 63 ± 5%, respectively, of initial body weight.

β-Adrenergic Receptor Number and Antagonist Affinity

The β-adrenergic antagonist [125I]cyanopindolol was used to determine the number and affinity of myocardial β-adrenergic receptors. Scatchard analysis demonstrated a single population of binding sites (Table 1) displaying an affinity consistent with earlier reports.17 Antagonist binding parameters were independent of the presence of guanine nucleotides (data not shown). No significant differences were observed among the different animal groups (Table 1).

β-Adrenergic Receptor and Stimulatory Guanine-Nucleotide–Binding Protein Interaction

Competition binding between ICYP and isoproterenol using myocardial membranes prepared from control rats demonstrated the existence of two affinity states (Figure 1, Table 2) where the high-affinity state constituted about 45%. Inclusion of the binding buffer of 0.1 mM Gpp(NH)p, a nonhydrolyzable GTP analogue, induced an affinity shift leaving all the receptors in the low affinity state. This affinity shift is believed17 to mirror activation of the stimulatory G protein with concomitant dissociation of the ternary complex made up of isoproterenol, β-adrenergic receptor, and G protein.

Three major differences were demonstrated by analogous competition-binding experiments performed in membranes from the treated rats. All the malnourished animals, irrespective of the cause, displayed a reduced number of high-affinity binding sites that exhibited an increased affinity toward isoproterenol and, in addition, showed either an attenuated (rats starved for >48 hours) or a reversed response to 0.1 mM Gpp(NH)p (Figures 2–4, Table 2). Experiments using GTP instead of the nonhydrolyzable analogue demonstrated similar findings (data not shown). The high-affinity binding sites in myocardial membranes derived from PCM and tumor-bearing rats were unresponsive to PCM and tumor-bearing rats were unresponsive to PCM and tumor-bearing rats were unresponsive to PCM and tumor-bearing rats were unresponsive to PCM and tumor-bearing rats were unresponsive to PCM.
nucleotides. The low-affinity sites displayed a slight increase in affinity versus isoproterenol and a limited guanine-nucleotide-induced affinity shift in membranes from PCM and tumor-bearing rats.

The time-course experiments in starved rats during 0–96 hours showed that although body weight was not reduced to a great extent until 96 hours, a shorter starvation period clearly affected β-adrenergic receptor affinity detectable after 48 hours (Table 2). No time-course–related dissociation between the three different effects on β-adrenergic receptors of starvation was apparent; that is, the increased agonist affinity, the decreased proportion of high-affinity sites, and the impaired sensitivity toward guanine nucleotides showed a similar time course.

Cholera-toxin–induced ADP-ribosylation was used as a means to assess relative differences in membrane levels of the stimulatory guanine-nucleotide-binding protein. The degree of incorporation of radioactive label was found to depend in a linear fashion on the added amount of membrane protein. Five control samples were run together on the same gel with five samples from starved (48 hour), PCM, or tumor-bearing rats. The same amount of protein was applied on the gel from the various samples. The control samples were defined as 100% concentration of the stimulatory GTP-binding protein and varied ±18%. Starved (48 hour), PCM, and tumor-bearing rats showed 108±22%, 98±27%, and 103±17%, respectively.

### Table 2. Effects of Malnutrition on Competition Between ICYP and Isoproterenol for Binding to Myocardial Membranes

<table>
<thead>
<tr>
<th>Animal group</th>
<th>No addition</th>
<th>100 μM Gpp(NH)p added</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RH (%)</td>
<td>KDh (nM)</td>
</tr>
<tr>
<td>Control</td>
<td>45±4</td>
<td>20±7</td>
</tr>
<tr>
<td>Starved 24 hours</td>
<td>47±6</td>
<td>22±5</td>
</tr>
<tr>
<td>48 hours</td>
<td>27±9</td>
<td>0.12±0.06t</td>
</tr>
<tr>
<td>96 hours</td>
<td>24±7</td>
<td>0.10±0.04f</td>
</tr>
<tr>
<td>Protein deprived</td>
<td>27±8</td>
<td>0.11±0.06f</td>
</tr>
<tr>
<td>Tumor bearing</td>
<td>19±7</td>
<td>0.11±0.04f</td>
</tr>
</tbody>
</table>

ICYP, iodocyanopindol.

**Kdh**/Kdl, number of high- and low-affinity sites; Kdh/Kdl, their corresponding affinities. Binding parameters calculated by regression analysis and corrected according to Cheng and Prusoff.13

*Addition of 0.1 mM Gpp(NH)p, a nonhydrolyzable GTP analogue, caused a significant change (p<0.001).

†p<0.001; differs significantly from the corresponding values in the control rats.

‡p<0.01; differs significantly from the corresponding values in the control rats.
**Muscarinic-Receptor-Binding Characteristics**

Myocardial as well as sinoatrial adenylate cyclase are under dual control: stimulation exerted by β-adrenergic and inhibition by muscarinic receptors. The properties of the muscarinic cholinergic receptors in rat myocardial membranes were explored by the tritiated antagonist QNB. Scatchard analysis revealed a single population of binding sites in rat myocardial membranes prepared from control animals as well as malnourished rats (Table 1). Neither the receptor density (B$_{max}$) nor dissociation constant (K$_D$) were influenced by the inclusion of 0.1 mM Gpp(NH)p in the incubation mixture.

Competition-binding curves obtained on control membranes with tritiated QNB and the muscarinic agonist carbachol using the incubation buffer described above can be resolved into two components, one with high (R$_H$) and one with low (R$_L$) affinity (Figure 5, Table 3). When 0.1 mM Gpp(NH)p was added to the incubation mixture, the R$_H$ state was undetectable (Figure 5), that is, all binding sites were in the R$_L$ state.

When the same set of experiments was carried out on rat myocardial membranes derived from malnourished animals, a significant difference was noted. When carbachol binding was resolved by computerized regression analysis, a super-high affinity population of muscarinic receptors became apparent, irrespective of the cause of malnutrition (Figures 6–8, Table 3). In spite of the addition of 0.1 mM Gpp(NH)p, a small percent of muscarinic receptors was retained (Figures 6–8) in the high-affinity state in membranes from malnourished rats ($p<0.001$). The affinity state distributions demonstrated in Figures 6–8 all differed significantly ($p<0.001$) from the corresponding control results in Figure 5.

**Modulation of the Activity of Adenylate Cyclase**

Adenylate cyclase activity was assayed by increasing concentrations of epinephrine. Maximal stimulation was achieved with 10 μM epinephrine in the presence of 0.1 mM Gpp(NH)p. Malnutrition did not affect the maximal response at 10 μM epinephrine nor the dose-response curve (Figure 9). Inhibi-
TABLE 3. Effects of Malnutrition on Competition Between QNB and Carbachol for Binding to Myocardial Muscarinic Receptors  

<table>
<thead>
<tr>
<th>Animal group</th>
<th>No addition</th>
<th>100 µM Gpp(NH)p added</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RSH (%)</td>
<td>KDH (µM)</td>
</tr>
<tr>
<td>Control</td>
<td>0±1</td>
<td>46±9</td>
</tr>
<tr>
<td>Starved 24 hours</td>
<td>0±1</td>
<td>43±8</td>
</tr>
<tr>
<td>Starved 48 hours</td>
<td>14±2</td>
<td>39±8</td>
</tr>
<tr>
<td>Starved 96 hours</td>
<td>17±3</td>
<td>36±6</td>
</tr>
<tr>
<td>Protein deprived</td>
<td>22±3*</td>
<td>0±0</td>
</tr>
<tr>
<td>Tumor bearing</td>
<td>19±2*</td>
<td>0±0</td>
</tr>
</tbody>
</table>

QNB, quinuclidinyl benzilate.
RSH, RSI, RL denote number of superhigh-, high-, and low-affinity sites, and KDH, KDH, KDL represent their corresponding affinities.

Binding parameters were calculated by regression analysis and corrected according to Cheng and Prusoff.13

*Addition of 0.1 mM Gpp(NH)p, a nonhydrolyzable GTP analogue, caused a significant change (p<0.001).
+p<0.01; differed from corresponding values in control rats.

Discussion
The heart of the malnourished host retains its capacity to respond to altered physiological demands in spite of a profound loss of cardiac contractile mass. This functional adaptation seems to involve adrenergic mechanisms4,18,19 and, consequently, suggests alterations in the adenylate cyclase system.

A major goal of investigators of adenylate cyclase has been to understand the sequence of molecular events required for transmembrane signaling. This process is initiated by agonist binding to the receptors and thus results in the stimulation of the catalytic moiety. Guanine nucleotides not only modulate the catalytic activity of adenylate cyclase but also influence agonist-receptor affinity. Ligand-binding studies of the β-adrenergic receptor,17 including computer modeling techniques, suggested the ternary complex model as the simplest explanation of the obtained data. In this model the β-adrenergic receptors show high affinity toward agonists if coupled to the stimulatory guanine-nucleotide-

FIGURE 6. [3H]Quinuclidinyl benzilate/carbachol competition binding in the absence (O) or presence (•) of 0.1 mM Gpp(NH)p, a nonhydrolyzable GTP analogue, on myocardial membranes derived from protein-deprived rats. Each data point represents the mean of the experiments performed in duplicate on each rat in this group. Each competition-binding experiment was analyzed by computerized regression analysis. Calculated binding parameters from different competition experiments were averaged and used for generating the occupancy-concentration curve. Insets demonstrate the affinity state distribution.

FIGURE 7. [3H]Quinuclidinyl benzilate/carbachol competition binding in the absence (O) or presence (•) of 0.1 mM Gpp(NH)p, a nonhydrolyzable GTP analogue, on myocardial membranes derived from tumor-bearing rats. Each data point represents the mean of the experiments performed in duplicate on each rat in this group. Each competition-binding experiment was analyzed by computerized regression analysis. Calculated binding parameters from different competition experiments were averaged and used for generating the occupancy-concentration curve. Insets demonstrate the affinity state distribution.
binding protein (G₃). Guanine nucleotides convert all the high-affinity receptors (Rₕ state) to the low-affinity state (Rₜ), which is believed to mirror the dissociation of the receptor-G₃ complex. The extent to which an agonist may stimulate the activity of adenylate cyclase correlates with the percent of β-adrenergic receptors in the Rₘ state, that is, equivalent to the number of receptors shifted in agonist affinity by guanine nucleotides. The experimental data obtained by purification of the regulatory guanine-nucleotide-binding proteins provide additional support for the idea that G₃ works as a shuttle that conveys information from the stimulatory receptors to the catalytic subunit of adenylate cyclase.

Our findings in rats indicate that β-adrenergic receptor number or antagonist affinity are not influenced by malnutrition. However, the coupling mechanism between the stimulatory guanine nucleotide binding protein and β-adrenergic receptor seems to be perturbed. Membranes from PCM and tumor-bearing rats contained a reduced number of high-affinity binding sites that displayed an approximately tenfold increase in agonist affinity. Moreover, the β-adrenergic receptors in these membranes reacted in an unusual way to guanine nucleotides. The experimental data obtained by purification of the regulatory guanine-nucleotide-binding proteins provide additional support for the idea that G₃ works as a shuttle that conveys information from the stimulatory receptors to the catalytic subunit of adenylate cyclase.

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Negative control of adenylate cyclase activity mediated by muscarinic receptors in rat myocardium was not influenced by malnutrition. The muscarinic receptor number and antagonist binding characteristics did not significantly differ due to the state of nutrition. Competition-binding data obtained in myocardial membranes from malnourished rats were best fitted by a three-site model as contrasted to a two-site model in the control group. This affinity state distribution has earlier been reported as a response to high concentrations of magnesium or manganese ions present in the incubation buffer but also after pretreatment with hydrocortisone both in vivo and in vitro and may reflect an altered receptor-inhibitory guanine-nucleotide-binding protein coupling.

Hormonal changes, other than adrenergic, are induced by malnutrition and might influence receptor function. An interaction by altered levels of thyroid hormones as well as steroids has been proposed. Intriguingly, hypothyroidism as well as...
hyperthyroidism has been reported\textsuperscript{29} to abolish the usually noted affinity shift of $\beta$-adrenergic receptors on addition of GTP analogues. Treatment with hydrocortisone produced muscarinic receptor changes similar to those reported here.\textsuperscript{23,24}

Regardless of the cause, malnutrition induces an increased sensitivity and reactivity to catecholamines, which has been demonstrated both clinically\textsuperscript{18} and in the experimental setting.\textsuperscript{419}

In conclusion, the data suggest that malnutrition modulates the interaction between myocardial receptors and their corresponding regulatory guanine-nucleotide–binding protein.

References


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\textbf{Key Words:} malnutrition \hspace{1em} myocardial receptors \hspace{1em} tumor \hspace{1em} adenylyl cyclase system \hspace{1em} competition binding
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