Further Studies on Experimental Atherosclerosis and Dietary Pyrimidines: Orotic Acid, Thiouracil, and Uracil in Male and Female Rats

By Louis C. Fillios, Sc.D., Chikayuki Naito, M.D., Stephen B. Andrus, M.D., and Alice M. Roach, A.B.

The comparative potencies of uracil and thiouracil in terms of thyroidal changes, hypercholesteremia, azotemia, and incipient atherosclerosis were determined in rats fed cholesterol and cholic acid. Higher dietary levels of uracil were required to produce changes similar to those seen with thiouracil. Certain dietary components related to uracil were also studied. Orotic acid was found to have a dramatic effect on female rats: it favored a markedly lower serum cholesterol level and less cardiovascular sudanophilia. When orotic acid was combined with uracil, the uracil-induced hypercholesteremia and atherogenesis were significantly inhibited, particularly in the females. Orotic acid also protected against the uracil-induced thyroid hyperplasia in these females.

The exaggeration of hypercholesteremia and atherogenesis in rats fed cholesterol and cholic acid with the goitrogenic agent, thiouracil, is well established. Such procedures have been also instrumental in producing myocardial infarcts in this animal. Recently it was shown that certain naturally occurring pyrimidine compounds potentiate the hypercholesteremia and cardiovascular lipid deposition incident to cholesterol feeding, and the most potent of these agents was found to be uracil, a constituent of ribonucleic acid and chemically related to thiouracil.

In the present report the effects of uracil and thiouracil on hypercholesteremia, azotemia, cardiovascular lipid deposition, and on thyroid weights are compared. Also, the influence of certain related metabolites are considered. Since orotic acid is a precursor in the synthesis of uracil, this compound was investigated as to its influence on those metabolic changes induced by dietary uracil. Furthermore, a comparison of the effects of these various dietary pyrimidines between male and female rats was carried out. It had been observed earlier that female rats are more susceptible to hypercholesteremia and incipient atherosclerosis. These studies appeared to be contradictory to observations made in humans, since adult men are believed to be more prone to hypercholesteremia and coronary atherosclerosis than women before age fifty. This purported species difference could not be explained within the dietary parameters heretofore employed in studying experimental atherosclerosis in the rat. An approach to resolving this apparent conflict was to consider other dietary components such as the purines and pyrimidines. The human intake in this country of both purines and pyrimidines is significant; at least 0.5 Gm. of these compounds are ingested daily by a large percentage of the population.

Methods

The basal regimen in these experiments is a modification of diets known to produce grossly visible endocardial sudanophilia and atheromatous lesions of the aorta and coronary arteries. This diet contains 1.5 per cent cholesterol, 0.5 per cent

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cholic acid, 20 per cent hydrogenated cottonseed oil, 20 per cent casein, 53.5 per cent sucrose, 0.2 per cent choline chloride, 0.1 per cent inositol, 4 per cent salts, and trace nutrients as previously described.10 This mildly atherogenic diet has been found to produce a hypercholesterolemia of approximately 300 mg. per cent in males, and of 500 mg. per cent in females in 5 weeks (normal rat serum total cholesterol: about 60 and 80 mg. per cent in the males and females respectively).5 In the present study a five-week assay period was adopted since experiences with thiouracil* and with uracil4 suggested that both these compounds will favor a significant endocardial sudanophilia in this time.

One hundred and sixty-five albino rats of the Charles River strain were housed, 5 or 6 to a cage, in a temperature controlled room (70 F); the animals were fed ad libitum. Blood samples were taken from each animal at the end of 2, 3, and 5 weeks of dietary treatment for the determination of the serum total cholesterol by the method of Carpenter et al.11 The bleeding at 5 weeks was carried out via cardiae puncture, the animals then being sacrificed. Serum urea was calculated from a spectrophotometric modification of the methods of Ormsby12 and Kawerau.13 The heart and aorta were opened in situ, excised, fixed in 10 per cent formalin, and stained with Sudan IV. The degree of endocardial sudanophilia was measured with the aid of a dissecting microscope equipped with an ocular grid as the area of visible sudanophilia affecting the region of the mitral and aortic valves. One hundred ocular grid units is equivalent to 3.41 mm² of surface. The major viscera were also preserved for histologic analysis (Hematoxylin-Eosin stain).

Five different levels of thiouracil and 5 of uracil were compared in rats fed the above diet, there being 5 to 6 rats in each group. Nine additional animals, fed only the basal atherogenic diet, were used as controls. Therefore, a total of 69 males, averaging 250 Gm. in weight, were placed on these various regimens. Thiouracil at the highest level was not tolerated, as evidenced by extreme anorexia during the first few days.

The second experiment, involving 31 females and 65 males, is concerned with the interactions of dietary uracil and orotic acid and sex. In addition to control groups receiving the basal atherogenic diet, each sex was represented by 5 dietary groups supplemented as follows: (a) 1 per cent uracil, (b) 1 per cent orotic acid, (c) 1 per cent uracil + 1 per cent orotic acid, (d) 0.075 per cent thiouracil, (e) 0.075 per cent thiouracil + 1 per cent orotic acid. There were 5 to 10 rats in each group.

In this second experiment the selection of the uracil and thiouracil doses was based on extrapolations made from the data in the first experiment. It had been estimated that a dietary level of thiouracil of 0.075 per cent will produce changes comparable to a level of 1 per cent uracil. However, exact comparisons between the 2 experiments are difficult, since the rats used in the second experiment are at least 1 month older than those in the first.

Included in the second experiment are 3 groups of male rats receiving in addition to the basal atherogenic diet supplements of: (a) 1 per cent thymine + 1 per cent uracil, (b) 1 per cent uracil, and (c) 2 per cent aspartic acid. The combination of thymine and uracil was tested in view of the previous finding that dietary supplementation with ribonucleic and deoxyribonucleic acids seemed to exert a protective action on endocardial lipid deposition.4

Results

Serum Urea

Rats normally maintain serum urea levels of about 30 mg. per cent. Apparently a significant increase in azotemia can be achieved in time with a dietary level of uracil of 1 per cent or higher; with lower dietary levels only small increments of increase were noted. Among the rats fed thiouracil, with dietary levels of 0.25 per cent or higher, progressive elevations in serum urea were noted; at the 1.0 per cent level a mean level of serum urea of 79 mg. per cent was observed at the end of 5 weeks (table 1).

Attempts to correlate these azotemic responses with pathologic changes in the kidney and the genitourinary tract were made. Certain animals, particularly those fed higher levels of thiouracil, displayed pathologic changes in the urinary tract, such as calcification within the renal tubules and bladder stone formation. Such changes were, however, quite inconstant and bore no apparent relationship to the degree of azotemia. Finally, no apparent correlation between the serum urea level and cardiovascular lipid deposition was observed.

Interestingly enough, the control female
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Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Terminal Serum Urea (mg. %)</th>
<th>Serum Cholesterol Response (mg. %)</th>
<th>Body Weight Response (%)</th>
<th>Thyroid Weight (mg.)</th>
<th>Endocardial Sudanoophilia (ocular grid units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (9)</td>
<td>278</td>
<td>+75</td>
<td>27.8</td>
<td>6.0</td>
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<tr>
<td>0.125% Uracil (5)</td>
<td>31</td>
<td>+35</td>
<td>31.1</td>
<td>7.9</td>
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<tr>
<td>0.25% Uracil (5)</td>
<td>32</td>
<td>+30</td>
<td>30.2§</td>
<td>20.5§</td>
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<tr>
<td>0.50% Uracil (6)</td>
<td>34</td>
<td>+37</td>
<td>43.0§</td>
<td>14.8§</td>
<td></td>
</tr>
<tr>
<td>1.00% Uracil (5)</td>
<td>41</td>
<td>+20§</td>
<td>44.8§</td>
<td>28.8§</td>
<td></td>
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<tr>
<td>2.00% Uracil (6)</td>
<td>42§</td>
<td></td>
<td>44.3§</td>
<td>26.0§</td>
<td></td>
</tr>
<tr>
<td>0.125% Thiouracil (5)</td>
<td>34</td>
<td>717§</td>
<td>52.5§</td>
<td>39.8§</td>
<td></td>
</tr>
<tr>
<td>0.25% Thiouracil (6)</td>
<td>45</td>
<td>1100§</td>
<td>79.9§</td>
<td>38.2§</td>
<td></td>
</tr>
<tr>
<td>0.50% Thiouracil (6)</td>
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<td>+1§</td>
<td>76.3§</td>
<td>30.8§</td>
<td></td>
</tr>
<tr>
<td>1.00% Thiouracil (6)</td>
<td>79§</td>
<td>729§</td>
<td>62.3§</td>
<td>37.6§</td>
<td></td>
</tr>
<tr>
<td>2.00% Thiouracil (6)</td>
<td>79§</td>
<td></td>
<td>44.3§</td>
<td>26.0§</td>
<td></td>
</tr>
</tbody>
</table>

( ) Number of surviving animals.

* The mean serum cholesterol burden is based on the average response derived from the levels observed at each interval of bleeding during the five week assay.

† (Final body weight—initial body weight/initial body weight) x 100; the initial body weight of these male rats averaged 260 Gm.

§ These values indicate only a suggestive difference (p<0.05 but >0.02).

§ These values indicate significant differences from the "control" values (p<0.02).

Rats developed higher serum urea levels than did the control males when fed the atherogenic regimen (table 2).

Serum Total Cholesterol

The addition of uracil to the above atherogenic diet at levels of 0.25 per cent or higher resulted in a significant exaggeration of the hypercholesteremic response (table 1). Apparently a maximal response can be attained at a dietary level of approximately 1.0 per cent; at a 2 per cent level the animals displayed a mild degree of anorexia, as evidenced by weight loss. In other studies from this laboratory (unpublished), hypercholesteremia has been induced in rats fed diets containing uracil, but without any other known hypercholesteremic stimuli such as cholesterol or cholic acid. For example, with a dietary level of 1.0 per cent, serum total cholesterol values approximately twice normal were observed in a few weeks, and the animals displayed thyroidal changes similar to those seen among the rats treated with uracil in the present report.

Among the rats fed thiouracil in the present experiment, a peak response in hypercholesteremia was seen at a dietary level of 0.25 per cent or less; higher levels of thiouracil did not increase this response significantly.

In the second experiment (Table 2) supplements of either urea, aspartic acid, or orotic acid had no marked effect on the hypercholesteremic response of male rats. The rats receiving a diet containing 1 per cent uracil had, as expected from the first experiment, a marked elevation in the serum cholesterol response. However, in the group which received 1 per cent uracil in addition to 1 per cent uracil, a protection against the uracil augmented hypercholesteremia was observed (p < 0.02). On the other hand, the addition of thymine did not seem to reverse the dietary uracil effect. When orotic acid was included in diets containing thiouracil, a milder protection against the expected hypercholesteremia occurred (p < 0.05); perhaps the level of thiouracil selected produced a hypercholesteremia so severe that the orotic acid effect was minimized in this latter comparison among these male rats.

Orotic acid has a remarkable effect in females. As shown by numerous other experi-
Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Terminal Serum Urea (mg. %)</th>
<th>Serum Cholesterol Response* (mg. %)</th>
<th>Body Weight Response† (%</th>
<th>Thyroid Weight (mg.)</th>
<th>Endocardial Sudanophilia (ocular grid units)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls (10)</td>
<td>33</td>
<td>284</td>
<td>+34</td>
<td>28.7</td>
<td>3.1</td>
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<tr>
<td>Orotic Acid (10)</td>
<td>37</td>
<td>424</td>
<td>+19</td>
<td>25.7</td>
<td>5.6</td>
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<tr>
<td>Uracil (10)</td>
<td>50§</td>
<td>669</td>
<td>+24</td>
<td>42.7§</td>
<td>19.2$</td>
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<tr>
<td>Uracil + Orotic Acid (10)</td>
<td>31</td>
<td>329</td>
<td>+25</td>
<td>38.1</td>
<td>3.5</td>
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<tr>
<td>Thiouracil (5)</td>
<td>46§</td>
<td>131§</td>
<td>+11</td>
<td>51.0§</td>
<td>19.6$</td>
</tr>
<tr>
<td>Thiouracil + Orotic Acid (5)</td>
<td>46§</td>
<td>631§</td>
<td>+8</td>
<td>38.9§</td>
<td>15.6$</td>
</tr>
<tr>
<td>Urea + Thymine (5)</td>
<td>—</td>
<td>536§</td>
<td>+24</td>
<td>30.3§</td>
<td>14.4$</td>
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<tr>
<td>Urea (5)</td>
<td>—</td>
<td>364</td>
<td>+35</td>
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<td>0.91</td>
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<tr>
<td>Aspartic Acid (5)</td>
<td>—</td>
<td>331</td>
<td>+38</td>
<td>22.3</td>
<td>1.51</td>
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<td>Controls (6)</td>
<td>45</td>
<td>910</td>
<td>+28</td>
<td>23.8</td>
<td>8.5</td>
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<tr>
<td>Orotic Acid (5)</td>
<td>47</td>
<td>299§</td>
<td>+12§</td>
<td>20.4</td>
<td>3.9§</td>
</tr>
<tr>
<td>Uracil (5)</td>
<td>39</td>
<td>1193</td>
<td>+8§</td>
<td>48.1§</td>
<td>38.8§</td>
</tr>
<tr>
<td>Uracil + Orotic Acid (5)</td>
<td>49</td>
<td>154§</td>
<td>+20§</td>
<td>22.5</td>
<td>1.5§</td>
</tr>
<tr>
<td>Thiouracil (5)</td>
<td>39</td>
<td>1882§</td>
<td>+4§</td>
<td>39.8§</td>
<td>36.8§</td>
</tr>
<tr>
<td>Thiouracil + Orotic Acid (5)</td>
<td>49</td>
<td>450§</td>
<td>−1§</td>
<td>45.2§</td>
<td>9.8</td>
</tr>
</tbody>
</table>

( ) Number of animals.

* The mean serum cholesterol burden is based on the average response derived from the levels observed at each interval of bleeding during the five week assay.
† (Final body weight—initial body weight/initial body weight x 100; the initial body weight of these males was 345 Gm.; that of the females, 255 Gm.
§ These values indicate only a suggestive difference (p<0.05 but >0.02).
$ These values indicate significant differences from the "control" values (p<0.02).

dences from this laboratory,5-7 the female rat is more susceptible to hypercholesteremia than the male when fed an atherogenic regimen. This difference was confirmed in the present study (p < 0.01). But when orotic acid was included, this sex difference was eliminated (table 2). Even more remarkable is the protection achieved with dietary orotic acid in those females also receiving uracil or thiouracil (p < 0.001).

Cardiovascular Sudanophilia

The amount of endocardial sudanophilia observed in these studies generally reflected the degree of elevation of the serum cholesterol. It was found that with increasing dietary levels of uracil, an increase in the degree of endocardial sudanophilia occurred. Among the rats fed thiouracil the degree of endocardial sudanophilia was distinctly higher than that seen in the above animals. This latter response appeared quite uniform, however, irrespective of the dietary level of thiouracil. These lesions involved the aortic and mitral valves, and the intervening endocardium. In both groups of animals, varying degrees of aortic sudanophilia were seen, generally associated with higher levels of endocardial sudanophilia. This aortic involvement, because of the diffuse nature of the changes, is difficult to quantitate; for this reason the aortic findings are not included in tables 1 and 2. The animals fed the 2 highest levels of uracil showed a degree of aortic involvement approaching that seen in these animals fed the lower levels of thiouracil. The animals receiving thiouracil did show some quantitative variations in aortic sudanophilia despite the uniform endocardial response, aortic involvement being most marked at the 0.25 and 0.5 per cent dietary levels. None of the groups receiving orotic acid showed any overt aortic disease.
It is interesting to note that either dietary urea or aspartic acid appeared to favor less endocardial sudanophilia than seen in the control males (p < 0.05). However, this observation remains to be substantiated by larger numbers of animals.

The endocardial sudanophilic changes related to orotic acid feeding generally reflected the serum cholesterol differences discussed above.

Thyroid Changes

As has been reported previously, uracil was found to have a distinct goitrogenic effect. Histologically the hyperplastic thyroid changes following uracil feeding are identical with those following thiouracil, though quantitatively less marked. On the basis of the data in table 1, it appears that the 2 highest levels of uracil tested resulted generally in changes in thyroid weight, body weight, and serum cholesterol levels which approach those seen with the lowest dietary levels of thiouracil employed. On the basis of these comparisons, thiouracil would appear to be at least 15 times as potent as uracil. Chemical analysis of the uracil employed revealed only traces of sulfur. Thus the changes induced by dietary uracil cannot be ascribed to potential contamination with thiouracil or some related sulfur compounds.* This, of course, does not eliminate the possibility that at some stage in the metabolism of uracil this compound might combine with dietary or endogenous sulfur to form a thiouracil-like compound.

It is of interest that hyperplasia of the thyroid following uracil feeding appeared more marked in females than in males, as evidenced both by increase in weight (table 2) and histologic response. What was of most interest was the protection against the uracil-induced increase in thyroid weight, especially among female animals, when orotic acid was included in the diet. These observations were supported by histologic findings; the thyroids of female rats fed both uracil and orotic acid were indistinguishable from those of the controls. Histologically, male rats responded similarly, though this protective action of orotic acid was only suggestive on an organ weight response basis (p ≤ 0.05).

No definite evidence of a protective action of orotic acid against thiouracil-induced thyroid hyperplasia could be found in either males or females on the basis of organ weight or histologic response. Among male rats, however, there was a suggestive protection as judged by thyroid weight response (p ≤ 0.05). Finally, among the animals receiving only the orotic acid supplement definite histologic changes were not seen.

Discussion

It has recently been demonstrated that uracil is a distinct goitrogen. This property of uracil appears unique among the naturally occurring pyrimidines that have been assayed to date. It is not known at present whether the mechanism of action is similar to that of thiouracil, i.e., by inhibiting the formation of thyroid hormone, primarily at the step of the protein binding of iodine. The possibility that dietary uracil might be thiolated within the body with the formation of a thiouracil-like compound cannot be excluded. A comparable phenomenon involving thiolation of dietary urea would not appear likely in view of the negative results of urea feeding (table 2). In any case, an important metabolite is capable of affecting thyroid physiology to the extent of favoring hypercholesteremia and cardiovascular lipid deposition in experimental animals. The possibility of an extrathyroidal action of thiouracil and related compounds must also be considered in interpreting these phenomena. It has been shown by S35 labeling that thiouracil may substitute in part for uracil in the ribonucleic acid moiety. The incorporation of unnatural uracil bases has been demonstrated in both microorganisms and mammalian cells. Thus it would seem possible that the composition of the cytoplasmic nucleic acids might be altered by excessive uracil feeding, for example, by the intro-

*Chemically pure uracil has also been fed, and the results are consistent with those mentioned herein. Chromatographic analyses of this uracil did not reveal any trace of thiouracil.

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duction into the nucleic acids of a thiolated uracil or some other unnatural base. Such considerations of potential biochemical alterations of the cell would allow for a wider concept of atherosclerosis than that which focuses primarily on the circulating serum lipids.

Regardless of the mode of action, the data presented raise some provocative questions. Does an imbalance in the dietary nucleic acids lead to metabolic dyscrasias favoring atherosclerosis? An excess of either dietary RNA or DNA has been shown to favor early lipid bearing lesions in animals fed cholesterol; on the other hand, when these 2 nucleic acids are fed together, the appearance of such lesions is minimized. 1 In the present data such a protective action was not clearly demonstrated when both uracil and thymine (the distinctive pyrimidines of the two compounds) were fed together at high levels. The present data do demonstrate a remarkable protective action of orotic acid against the effects of uracil feeding. Thus, serum cholesterol elevation and endocardial sudanophilia are reduced. These effects are distinctly more marked in female rats than in males. Indeed, in the former, the increase in hyperplasia incident to uracil feedings was also obliterated. This action of orotic acid might be explained by virtue of its preferential position in the pathway of uridine-5-phosphate.

We as yet have no explanation for perhaps the most interesting finding in terms of orotic acid, namely its ability to lower markedly serum cholesterol levels among female rats fed the basal atherogenic diet.

This phenomenon is accompanied by a reduction in endocardial sudanophilia and in the absence of apparent thyroid changes. The very distinctly higher serum cholesterol response of female rats fed cholesterol as compared with males is a well documented finding. 5-7 In effect, orotic acid feeding has at least eliminated this previously observed sex-linked difference. Such a reversal phenomenon is of particular interest in view of the apparent discrepancies between the human disease and the experimental counterpart as to sex-linked differences. Thus, an experimental approach avails itself which may perhaps tie together some of the contrasting aspects of the human disease, namely the dietary, gonadal, thyroidal, and possibly the genetic.

Summary

The recent observation that uracil potentiates thyroid hyperplasia, hypercholesteremia, and increased cardiovascular lipid deposition was confirmed. A comparison of uracil with thiouracil was made at 5 dietary levels. On the basis of these comparisons, it was extrapolated that thiouracil is at least 15 times more potent than uracil in causing the above changes. Otherwise the tissue and serum changes initiated by uracil feeding were similar to those seen when thiouracil is fed. The possibility that some of the dietary uracil may be thiolated to form a thiouracil-like metabolite has been considered in discussing these comparisons.

Other compounds related to uracil metabolism were also assayed in rats fed cholesterol and cholic acid. Dietary urea and aspartic acid had no effect on the thyroid or the serum cholesterol level, although both these substances had a mild protective effect on the amount of lipid deposited in the endocardium. On the other hand, orotic acid had a marked effect in both male and female rats.

The earlier observation that the female rat is more susceptible to hypercholesteremia and incipient atherosclerosis when fed diets containing cholesterol and cholic acid was repeated here. When such diets, however, also contain orotic acid, such a sex difference could not be shown. Furthermore, the uracil-induced hypercholesteremia, thyroid hyperplasia, and cardiovascular sudanophilia are inhibited when dietary orotic acid is included. This phenomenon with orotic acid is distinctly more marked in female rats, suggesting that a study of pyrimidine metabolism may be a profitable approach in explaining the protection of the human female against coronary artery disease during the pre-menopausal years.
ATHEROSCLEROSIS AND DIETARY PYRIMIDINES

Acknowledgment

We wish to thank Miss Barbara Blayton, Mr. Bruce Dorr, and Miss Peggy Putnam for their assistance, and Mr. Thomas Faherty for his microscopic preparations.

Summario in Interlingua

Essa confermat le recente observation che uracil effectua un potentiation de hyperplasia thyroide, de hypercholesterolemia, e del deposition cardiovascular de lipidio. Esse effectuare un comparison inter uracil e thiouracil a cinque nivellos dietari. Le resultatos de iste comparison permitteva le extrapolation quo thiouracil es al minus 15 vices plus potente que uracil in su capacitate de effectuer le supra-mentionate alterationes. Alteremente, le alterationes del histoe e del sero que esseva initiate per uracil dietari essera fariile a illos observate post le administration de thiouracil dietari. Le possibilitate che un parte del uracil dietari es subjicite a un processo de thiolation con le resultato del formation de un metabolito thiouraciloide es prendite in consideration in le discussion del comparison del duo agentes.

Altre compositos relationate al metabolismo de uracil esseva etiam studiate in rattos recipiente cholesterol e acido cholic. Uraca e acido aspartic in le dieta habeva nullo effecto super le stato del thyroide e super le nivello serai de cholesterol, ben que amb le iste substantias esseva un leve grado de activitate protectori con respecto al quantitate de lipidio che es deponite in le endocardio. Del alte intero, acido orotic habeva un marcate tal effecto in rattos mascule e etiam in rattos feminin.

Essa confermat le recente reportate observation che le ratto feminin es plus susceptibile de contralar hypercholesterolemia e atherosclerosis inicidente quando le dieta del animals continue cholesterol e acido cholic. Tanan, quando un tal dieta contina in plus acido orotic, le observatione differente inter le sexos non poteva esser observate. Etiam, le hypercholesterolemia, le hyperplasia thyroide, e le sudanophilia cardiovascular le quales es inducite per uracil es inhibit quando acido orotic es includite in le dieta. Iste effecto de acido orotic es distinctemente plus marcate in rattos feminin, un facto che suggerisce che le studio del metabolismo de pyrimidinas es possibilmente un bon methodo pro effortios de explicar le facto che le feminina human es protegite contra morbo de arteria coronari durante le annos pre-menopausal.

References


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