THE EXCRETION OF METABOLITES OF PROGESTERONE-21-C\(^{14}\) AFTER INTRAGASTRIC ADMINISTRATION TO RATS*

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Our interest in the relative inactivity of progesterone by oral administration reported by several investigators (1–4) has led us to utilize progesterone-21-C\(^{14}\) to ascertain whether the diminished activity could be related to absorption from the gastrointestinal tract. Since our experiments clearly showed that the metabolites were excreted more rapidly in urine than Grady et al. (5, 6) had observed for progesterone administered by the intramuscular route, a complete set of experiments comparable to those previously published, except for the mode of administration, is reported in this paper. In addition to the types of animals used by Grady et al., data are included for rats which had been subjected to a sham operation.

EXPERIMENTAL

Excretion of Radioactivity in Bile, Urine, Feces, and Expired Air after Intragastric Administration of Progesterone-21-C\(^{14}\).—In all experiments, spayed adult female albino rats from the St. Louis University colony, weighing from 250 to 350 gm., were used. In order to compare the rate of excretion after intragastric administration with that after intramuscular injection under similar conditions (5), 0.5 mg. of progesterone-21-C\(^{14}\) (a physiological amount for intramuscular and subcutaneous administration (7)) was given to four types of rats, namely, control (NC), operated by sham (OC), bile fistula (BF), and bile duct-ligated (DL). After intragastric administration of the steroid in 1 ml. of 50 per cent ethanol, the expired

* A preliminary report embodying some of the data contained in this paper was presented at the meeting of the Federation of American Societies for Experimental Biology in Chicago, 1953. The material presented herein is taken from a thesis submitted to the Graduate School of St. Louis University by Nai-hsuan Chang Shen in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Biochemistry.

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CO₂ (NC rats only), feces, urine, and bile (BF rats only) were collected at regular intervals for a 4 day period and analyzed for their radioactive contents. All samples were assayed for radioactivity as described previously.

Table I

<table>
<thead>
<tr>
<th>Type of rat</th>
<th>Rat No.</th>
<th>Recovery of administered C¹⁴ in excreta*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Expired CO₂</td>
</tr>
<tr>
<td>Control (NC)</td>
<td></td>
<td>per cent</td>
</tr>
<tr>
<td>1</td>
<td>13.6</td>
<td>28.4</td>
</tr>
<tr>
<td>2</td>
<td>15.6</td>
<td>20.2</td>
</tr>
<tr>
<td>3</td>
<td>14.4</td>
<td>32.9</td>
</tr>
<tr>
<td>Average</td>
<td>14.5</td>
<td>27.2</td>
</tr>
<tr>
<td>Operated by sham</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(OC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>38.6</td>
<td>53.6</td>
</tr>
<tr>
<td>2</td>
<td>37.9</td>
<td>48.2</td>
</tr>
<tr>
<td>3</td>
<td>37.7</td>
<td>55.6</td>
</tr>
<tr>
<td>Average</td>
<td>38.1</td>
<td>52.5</td>
</tr>
<tr>
<td>Bile fistula (BF)</td>
<td>1†</td>
<td>36.6</td>
</tr>
<tr>
<td>2</td>
<td>27.3</td>
<td>6.3</td>
</tr>
<tr>
<td>3</td>
<td>38.5</td>
<td>8.7</td>
</tr>
<tr>
<td>Average</td>
<td>34.1</td>
<td>6.9</td>
</tr>
<tr>
<td>Ligated bile duct (DL)</td>
<td>1</td>
<td>75.8</td>
</tr>
<tr>
<td>2</td>
<td>85.7</td>
<td>10.0</td>
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<td>3</td>
<td>79.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Average</td>
<td>80.3</td>
<td>10.2</td>
</tr>
</tbody>
</table>

* The excreta were collected for 4 days except as noted.
† The excreta of this animal were collected for a 5 day period. The excretion on the 5th day was less than 2 per cent.

(5); those samples of weak or questionable radioactivity were counted with a gas flow counter.

The percentages of the administered radioactivity excreted in bile, urine, feces, and expired C¹⁴O₂ during the 4 day period are given in Table I. It is apparent that the recovery of C¹⁴ (from 86 to 107 per cent) in the excreta in most cases was approximately quantitative. NC rats excreted from 14 to 16 per cent of the administered radioactivity in the expired air, indicating that the side chain from some of the labeled hormone was oxidatively...
removed. From 20 to 33 per cent was recovered in the urine and from 44 to 64 per cent in the feces. OC animals excreted about 38 per cent of the administered C\textsuperscript{14} in the urine and from 48 to 56 per cent in the feces. BF rats excreted from 57 to 65 per cent of the administered C\textsuperscript{14} in the bile, from 6 to 9 per cent in the feces, and from 27 to 39 per cent in the urine. DL rats excreted from 76 to 86 per cent of the administered radioactivity in the urine and from 7 to 14 per cent in the feces.

The excretory pathways of progesterone metabolites in these experiments are similar to those reported by Grady et al. (5) after intramuscular administration and by Riegler et al. (8) and Barry and associates (9) after intraperitoneal injection. The liver, intestinal tract, kidney, and lung were the main organs for excretion of metabolites; the major source of fecal C\textsuperscript{14} in the first two groups of animals (NC and OC) would seem to be the bile, as shown by the excretion of large amounts of C\textsuperscript{14} in the bile of the bile fistula rats. However, when the bile duct was ligated, the kidney assumed the major function of excretion.

The daily excretion of C\textsuperscript{14} is depicted in Fig. 1. In both the NC and OC rats, over 80 per cent of the administered radioactivity was excreted during
the 48 hour period following administration. The excretion appears to be somewhat more rapid in the NC rats, but this may be due to the fact that C\textsuperscript{14}O\textsubscript{2} was not determined in the expired air in OC rats. The rats with cannulated bile ducts excreted C\textsuperscript{14} as rapidly as the normal controls. Rats having ligated bile ducts excreted the metabolites less slowly than the other groups. It seems unlikely that this resulted from impaired absorption due to the inhibition of secretion of bile into the intestine, since the bile was also diverted from its normal channel in BF rats. Moreover, Hoffman, Masson, and Desbarats (10) found that after the administration of the same weight of progesterone by gavage a larger amount of pregnanediol was excreted in the urines of rabbits having transected bile ducts than in the urines of normal animals.

Since C\textsuperscript{14} was found in expired air of normal control rats, their urines were examined for C\textsuperscript{14}O\textsubscript{2} and urea-C\textsuperscript{14} in a closed system under conditions which gave quantitative recovery of CO\textsubscript{2} from Na\textsubscript{2}CO\textsubscript{3}; no C\textsuperscript{14}O\textsubscript{2} could be detected. After incubation of another aliquot of urine with urease, C\textsuperscript{14}O\textsubscript{2} was found only in the urines which had been collected during the first 24 hour period. The values were 0.45, 0.04, and 0.17 per cent of the radioactive carbon which had been given intragastrically.

**DISCUSSION**

After the intragastric administration of radioactive progesterone, the metabolites are excreted more rapidly than after intramuscular injection. This is probably due to two factors: (a) more rapid absorption from the intestines than from the intramuscular site, and (b) more effective presentation to the metabolic functions of the liver by the portal blood than by the general systemic circulation. The more rapid elimination (42 per cent) in bile during the first 24 hours after administration than in Grady's experiments (27 per cent) is consonant with both factors. Moreover, Sommerville and Marrian (11) have reported that pregnanediol is excreted in the urine of men more rapidly after oral administration than after intramuscular injection. That the liver plays an important rôle in the metabolism of progesterone has been shown by a number of investigators (12–17). However, until it has been shown that progesterone is absorbed unchanged from the gastrointestinal tract, it is impossible to evaluate completely the rôle of the liver in the relative inactivity of progesterone by oral administration.

**SUMMARY**

1. After intragastric administration of progesterone-21-C\textsuperscript{14} to normal rats, approximately 15 per cent of the administered radioactivity was eliminated in the expired air, 30 per cent in the urine, and 55 per cent in the
feces. In animals with cannulated bile ducts, the bile served as the major route of excretion, while, in animals with ligated bile ducts, the kidney assumed this function.

2. Metabolites of progesterone were excreted more rapidly after intragastric than after intramuscular administration, which might explain, in part, the relative inactivity of orally administered progesterone.

3. The appearance of C\textsuperscript{14} in expired air and in urinary urea indicates that oxidative scission of the side chain of progesterone-21-C\textsuperscript{14} occurred, with subsequent fixation of carbon dioxide.

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