The catecholamine response to spaceflight: role of diet and gender

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Stein, T. P., and C. E. Wade. The catecholamine response to spaceflight: role of diet and gender. Am J Physiol Endocrinol Metab 281: E500–E506, 2001.— Compared with men, women appear to have a decreased sympathetic nervous system (SNS) response to stress. The two manifestations where the sexual dimorphism has been the most pronounced involve the response of the SNS to fluid shifts and fuel metabolism during exercise. The objectives of this study were to investigate whether a similar sexual dimorphism was found in the response to spaceflight. To do so, we compared catecholamine excretion by male and female astronauts from two similar shuttle missions, Spacelab Life Sciences 1 (SLS1, 1991) and 2 (SLS2, 1993) for evidence of sexual dimorphism. To evaluate the variability of the catecholamine response in men, we compared catecholamine excretion from the two SLS missions against the 1996 Life and Microgravity Sciences Mission (LMS) and the 1973 Skylab missions. Results: No gender- or mission-dependent changes were found with epinephrine. Separating out the SLS1/2 data by gender shows that norepinephrine excretion was essentially unchanged with spaceflight in women (98 ± 10%; n = 3) and substantially decreased with the men (41 ± 9%; n = 4, P < 0.05). Data are a percentage of mean preflight value ± SE. Comparisons among males demonstrated significant mission effects on norepinephrine excretion. After flight, there was a transient increase in norepinephrine but no evidence of any gender-specific effects. We conclude that norepinephrine excretion during spaceflight is both mission and gender dependent. Men show the greater response, with at least three factors being involved, a response to microgravity, energy balance, and the ratio of carbohydrate to fat in the diet.

Although the majority of astronauts are men, the proportion of female astronauts is increasing. Future missions, including long-duration missions on the space station and eventually to Mars, are expected to include both men and women. Yet few studies have addressed the question of whether there are gender differences in the responses to spaceflight. There may well be. In recent years, a number of studies have shown that there is sexual dimorphism in the neuroendocrine and metabolic responses to physiological stress (11, 20). Compared with men, women appear to have a decreased sympathetic nervous system response to stress. The two manifestations where the sexual dimorphism has been the most pronounced involve the response of the sympathetic nervous system to fluid shifts and altered fuel metabolism during exercise, both of which are altered with spaceflight.

Entry into earth orbit causes a shift of water from the lower body to the upper body; the reverse occurs on reentry. On the ground, models of the fluid shifts have revealed gender-based differences in baseline cardiovascular function (14, 16), in the response to exercise (3, 21) and to bed rest (45) and the responses to orthostatic stress such as what occurs after going from the supine to erect positions (18, 47).

Apart from the well known fact that women tend to have more body fat than men, there are differences in how men and women mobilize fat (22, 35). The counterregulatory response to fasting and insulin-induced hypoglycemia is smaller in women than in men (1, 12, 13). Fuel metabolism during exercise is also different. When energy needs are high, as during exercise, women oxidize more lipid and less carbohydrate than men (8, 20, 30, 34). Furthermore, exercise is associated with significantly greater increases in epinephrine and norepinephrine secretion in men than women (12, 20).

Thus there is a considerable body of evidence to suggest that there is a sexual dimorphism in the response to a perturbation of homeostasis, be it in fluid/cardiovascular or energy metabolism. The objectives of this study were to investigate whether a similar sexual dimorphism is found in the response to spaceflight. To do so, we compared catecholamine excretion by male and female astronauts from two shuttle missions, the two similar Spacelab Life Sciences (SLS) missions, 1 (SLS1, 1991) and 2 (SLS2, 1993), for evidence of sexual dimorphism. To further evaluate the variability of the catecholamine response in men, we compared catecholamine excretion from the two SLS missions against the 1996 Life and Microgravity Sciences Mission (LMS) and the first 12 days of the 1973 Skylab missions.

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Skylab was a prototype space station that consisted of three similar missions of 28, 56, and 84 days (28).

METHODS

Urine Sample Collections

Twenty-four-hour urines were collected before, during, and after spaceflight on the payload crew members of space shuttle missions SLS1, SLS2, and LMS. Dietary intake before, during, and after spaceflight was measured (for details, see Refs. 42–44). The urine volumes collected from these missions were divided among several investigators. On SLS1 and SLS2, there were a number of common assays to one or more investigator teams. The common assays were done by NASA, and NASA provided the results to the other groups as part of a data-sharing agreement. Among the common group of analyses were the urinary catecholamines. For the purposes of this study, the data set from SLS1/2 was incomplete, because it included data only from subjects who participated in an experiment to study fluid regulation (26). One subject flew on both missions, and only the samples from SLS1 were analyzed by NASA. For this study, we analyzed the samples from the second mission, SLS2, and LMS. We did all of the catecholamine analyses on the urine samples from the LMS crew by HPLC and electrochemical detection. Creatinine analyses were available from our previous studies.

Statistical Analysis

Data in the text, tables, and figures are means ± SE, with the number of subjects in parentheses. Flight day 1 was not included in any of the analyses because of incomplete sample collection for some subjects and motion sickness. Statistical analyses were done by t-tests or one-way analysis of variance, as appropriate. Significance was accepted at \( P < 0.05 \).

RESULTS

SLS1 and SLS2 were very similar shuttle missions. Data from shuttle flights SLS1 and SLS2 are often combined to give a larger sample size (9, 26, 40, 41). SLS1 was a 9-day mission, and SLS-2 was a reflight of SLS1 but with measurements made up to day 12 of the 16-day mission. The 17-day LMS shuttle flight was flown in 1996. One subject flew twice. The responses for this subject were similar on the two missions. On SLS1, the subject’s inflight norepinephrine excretion was 96% of preflight; on SLS2 it was 91%. Because of the close agreement between the two missions, there is no effect on the statistical significance of the data with the use of either the mean or the individual values from SLS1/2. We used the data set from the second mission for this subject because more data (12 vs. 9 days) were available.

Tables 1 and 2 summarize the anthropometric and dietary data for the SLS1/2 and LMS shuttle missions (42, 43). The values for nitrogen balance are estimates, because they are based on urinary nitrogen and do not include fecal nitrogen losses. All of the astronauts lost weight, although the LMS astronauts lost much more weight than the SLS1/2 crew members (Table 1). Nitrogen balance decreased inflight on all missions, with the decrease being greatest for the LMS mission (Table 2).

Table 3 summarizes the effect of spaceflight on norepinephrine and epinephrine excretion for the two missions. No spaceflight-related changes were found with epinephrine. Overall norepinephrine excretion was decreased inflight on both SLS1/2 and LMS. Separating out the SLS1/2 data by gender shows that norepinephrine excretion was essentially unchanged with spaceflight in women and substantially decreased with the men (Table 3 and Fig. 1). The difference between the men and women on SLS1/2 was statistically significant \( P < 0.05 \). The rate of norepinephrine excretion was relatively constant with time in earth orbit (Figs. 1 and 2). After flight, there was a 1- to 2-day increase in norepinephrine but no evidence of any gender effects (Table 3); neither was there any difference in norepinephrine excretion on subsequent days postflight.

Figure 2 shows the time course of the norepinephrine changes during spaceflight for the men on SLS1/2, LMS, and the three Skylab missions. It is apparent from the figure that there was considerable variation in norepinephrine excretion between missions for the men. The variation appears to be mission rather than subject dependent. There were also differences in energy intake and nitrogen balance between the two missions (Table 4).

DISCUSSION

The Database

The data set consists of three independent sets of measurements.

The SLS1/2 mission. With the exception of the second sample set from the subject who flew twice, the SLS1/2 values were analyzed within a few weeks of collection. The other set from this subject was analyzed by us some 6 yr later.

The LMS mission. The urines from the LMS mission and the exception mentioned above had been stored for 4–6 yr at −70°C before being analyzed. As a consequence, they had lost some of their activity. Because all samples were treated the same, the data are still usable for comparative purposes. For the one subject who was studied twice, the absolute values were different with the NASA-provided SLS1/2 values (SLS1, analyzed in 1991, preflight 4.6 ± 0.4 nM·kg−1·day−1, 226 ± 24 nM·g creatinine·day−1) being greater than the later (SLS2, analyzed in 2000, preflight 1.5 ± 0.1 nM·kg−1·day−1, 77 ± 5 nM·g creatinine·day−1). Nevertheless, the change with spaceflight was the same (96 vs. 91% of the preflight value for the two missions).

Table 1. Body weight changes for SLS1/2 and LMS missions with spaceflight

<table>
<thead>
<tr>
<th>Mission</th>
<th>Preflight</th>
<th>Postflight</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLS1/2</td>
<td>72.7 ± 3.1</td>
<td>71.6 ± 3.2</td>
<td>−1.1 ± 0.4*</td>
</tr>
<tr>
<td>SLS1/2</td>
<td>74.1 ± 3.9</td>
<td>73.6 ± 4.2</td>
<td>−0.5 ± 0.6</td>
</tr>
<tr>
<td>LMS</td>
<td>70.9 ± 6.0</td>
<td>69.1 ± 5.6</td>
<td>−1.8 ± 0.6</td>
</tr>
</tbody>
</table>

Values are means ± SE. SLS1/2, Spacelab Life Sciences missions 1 and 2; LMS, Life and Microgravity Sciences mission; m, males; f, females. * \( P < 0.05 \) vs. preflight.
bers by Leach et al. (26) concluded that the overall
decrease was limited to the Skylab 4 crew (Fig. 3). A
decrease was observed, but when broken out by mission, the
response was mission dependent. We shall discuss the variability in
nepinephrine response was reduced on the LMS crew
members (Table 3 and Fig. 2, \( P < 0.05 \)). Three effects
acting in synergy can explain the variability in nepinephrine
excretion by men in flight.

\[ \text{Decreased sympathetic response to the fluid shifts.} \]

The first report of nepinephrine excretion in flight
was from the 1973 Skylab missions (28). Overall, a
trend toward a decrease in norepinephrine excretion
was observed, but when broken out by mission, the
decrease was limited to the Skylab 4 crew (Fig. 3). A
subsequent report on seven of the SLS1/2 crew members
by Leach et al. (26) concluded that the overall
excretion of norepinephrine was reduced in flight.

\[ \text{Values are means} \pm \text{SE. RO + R1 is the mean value for the 1st 2 days after landing.} \]

### Table 2. Dietary intake and nitrogen balance before, during, and after spaceflight on the SLS1/2 and LMS shuttle missions

<table>
<thead>
<tr>
<th>Mission/Period</th>
<th>Energy Intake, ((m+f, n = 7)) kcal·kg(^{-1})·day(^{-1})</th>
<th>N Balance, kg·day(^{-1})</th>
<th>Energy Intake, ((m, n = 4)) kcal·kg(^{-1})·day(^{-1})</th>
<th>N Balance, kg·day(^{-1})</th>
<th>Energy Intake, ((f, n = 3)) kcal·kg(^{-1})·day(^{-1})</th>
<th>N Balance, kg·day(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SLS1/2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preflight</td>
<td>39.1 ± 3.1</td>
<td>44 ± 6</td>
<td>42.0 ± 4.9</td>
<td>49 ± 8</td>
<td>35.3 ± 4.7</td>
<td>39 ± 11</td>
</tr>
<tr>
<td>Inflight</td>
<td>31.6 ± 1.8</td>
<td>25 ± 3*</td>
<td>33.4 ± 1.6</td>
<td>22 ± 6</td>
<td>29.3 ± 1.2</td>
<td>29 ± 6</td>
</tr>
<tr>
<td>R + 0 to R + 1</td>
<td>37.3 ± 3.6</td>
<td>55 ± 16</td>
<td>41.7 ± 3.7</td>
<td>44 ± 12</td>
<td>36.4 ± 2.9</td>
<td>67 ± 5</td>
</tr>
<tr>
<td>R + 0 to R + 6</td>
<td>39.4 ± 2.5</td>
<td>52 ± 59</td>
<td>40.4 ± 4.4</td>
<td>37 ± 8</td>
<td>35.6 ± 3.4</td>
<td>66 ± 9</td>
</tr>
<tr>
<td><strong>LMS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preflight</td>
<td>37.1 ± 3.2</td>
<td>59.8 ± 13.8</td>
<td>24.4 ± 1.4</td>
<td>-27.8 ± 4.8*</td>
<td>31.8 ± 3.6</td>
<td>38.0 ± 38.7</td>
</tr>
<tr>
<td>Inflight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36.6 ± 3.2</td>
<td>50.6 ± 14.8</td>
</tr>
</tbody>
</table>

Values are means \(\pm\) SE. \(RO + R1\) is the mean value for the 1st 2 days after landing. \(*P < 0.05\) vs. preflight.

### Table 3. Norepinephrine and epinephrine excretion before, during, and after spaceflight on the SLS1/2 and LMS shuttle missions

<table>
<thead>
<tr>
<th>Mission/Period</th>
<th>Creatinine, mg·kg(^{-1})·day(^{-1})</th>
<th>NE, nmol·kg(^{-1})·day(^{-1})</th>
<th>nmol/g creat</th>
<th>Epi, nmol·kg(^{-1})·day(^{-1})</th>
<th>nmol/g creat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SLS1/2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preflight</td>
<td>21.5 ± 1.7</td>
<td>9.46 ± 3.86</td>
<td>453 ± 119</td>
<td>0.99 ± 0.10</td>
<td>48.9 ± 5.4</td>
</tr>
<tr>
<td>Inflight</td>
<td>18.1 ± 1.8</td>
<td>4.23 ± 0.67*</td>
<td>247 ± 50*</td>
<td>0.86 ± 0.14</td>
<td>45.4 ± 4.9</td>
</tr>
<tr>
<td>R + 0 to R + 1</td>
<td>20.1 ± 1.8</td>
<td>21.87 ± 6.27</td>
<td>1286 ± 459</td>
<td>3.59 ± 3.26</td>
<td>132.1 ± 46.2</td>
</tr>
<tr>
<td>R + 0 to R + 6</td>
<td>19.6 ± 2.0</td>
<td>15.03 ± 4.52</td>
<td>791 ± 257</td>
<td>1.30 ± 0.54</td>
<td>77.5 ± 28.0</td>
</tr>
<tr>
<td><strong>SLS1/2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preflight</td>
<td>24.7 ± 0.6</td>
<td>11.56 ± 4.96</td>
<td>481 ± 207</td>
<td>1.05 ± 0.11</td>
<td>44.4 ± 3.8</td>
</tr>
<tr>
<td>Inflight</td>
<td>21.3 ± 1.9</td>
<td>3.48 ± 1.03*</td>
<td>158 ± 36*</td>
<td>0.94 ± 0.24</td>
<td>42.7 ± 7.3</td>
</tr>
<tr>
<td>R + 0 to R + 1</td>
<td>22.6 ± 0.6</td>
<td>23.30 ± 9.75</td>
<td>1052 ± 429</td>
<td>3.70 ± 3.41</td>
<td>121.5 ± 53.8</td>
</tr>
<tr>
<td>R + 0 to R + 6</td>
<td>22.4 ± 0.9</td>
<td>16.95 ± 7.35</td>
<td>685 ± 309</td>
<td>1.59 ± 0.86</td>
<td>71.0 ± 32.4</td>
</tr>
<tr>
<td><strong>SLS1/2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Preflight</td>
<td>17.9 ± 2.2</td>
<td>6.66 ± 1.02</td>
<td>414 ± 109</td>
<td>0.91 ± 0.22</td>
<td>54.9 ± 10.0</td>
</tr>
<tr>
<td>Inflight</td>
<td>14.0 ± 0.8</td>
<td>5.24 ± 0.42*</td>
<td>365 ± 53</td>
<td>0.76 ± 0.16</td>
<td>49.1 ± 7.0</td>
</tr>
<tr>
<td>R + 0 to R + 1</td>
<td>16.7 ± 3.5</td>
<td>19.97 ± 8.98</td>
<td>1599 ± 1011</td>
<td>3.44 ± 3.24</td>
<td>146.2 ± 94.8</td>
</tr>
<tr>
<td>R + 0 to R + 6</td>
<td>14.8 ± 2.7</td>
<td>12.48 ± 5.42</td>
<td>951 ± 502</td>
<td>0.93 ± 0.55</td>
<td>86.2 ± 57.7</td>
</tr>
<tr>
<td><strong>LMS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preflight</td>
<td>21.3 ± 1.8</td>
<td>1.55 ± 0.36</td>
<td>70.9 ± 11.3</td>
<td>0.38 ± 0.03</td>
<td>18.7 ± 2.4</td>
</tr>
<tr>
<td>Inflight</td>
<td>17.1 ± 1.01</td>
<td>0.86 ± 0.15*</td>
<td>49.6 ± 7.4*</td>
<td>0.29 ± 0.03</td>
<td>16.8 ± 1.6</td>
</tr>
<tr>
<td>R + 0 to R + 1</td>
<td>22.5 ± 1.5</td>
<td>1.84 ± 0.26</td>
<td>84.6 ± 11.8</td>
<td>0.44 ± 0.04</td>
<td>20.0 ± 1.8</td>
</tr>
<tr>
<td>R + 0 to R + 6</td>
<td>19.9 ± 1.0</td>
<td>2.03 ± 0.33</td>
<td>102.3 ± 14.5</td>
<td>0.33 ± 0.05</td>
<td>117.2 ± 3.7</td>
</tr>
</tbody>
</table>

Values are means \(\pm\) SE. NE, norepinephrine; Epi, epinephrine. \(*P < 0.05\) vs. preflight; \(\dagger P < 0.05\) for the change from preflight according to gender.
LMS and SLS1/2 men (Fig. 2). Finding a difference between two spaceflight missions is not an artifact. Our reexamination of the earlier Skylab data revealed similar differences among the three Skylab missions (Fig. 2). As with SLS1/2 and LMS, norepinephrine excretion on Skylab varied with mission rather than subject. We have previously reported that dietary intake varied in a similar manner with mission (Fig. 3), with the cause of the difference being the amount of exercise required of the crew (41).

It is clear from Figs. 2 and 3 that the variation for both norepinephrine excretion and energy intake is between missions rather than subjects. The relevant point to the present discussion is that the differential norepinephrine response cannot be attributed to the fluid shifts or other cardiovascular-related changes. The fluid shifts and cardiovascular responses are unique to microgravity, and the microgravity environment was the same for all missions. The parallels between Figs. 2 (norepinephrine) and 3 (dietary intake) suggest that the variability of the norepinephrine response is related to fuel metabolism. The two aspects of fuel metabolism that can influence norepinephrine metabolism are energy balance and the ratio of glucose to fat in the diet.

Energy balance. In previous analyses of differences in protein losses between the SLS1/2 and LMS missions, we showed that the missions were, in fact, very different in terms of dietary intake, workload, and energy balance (41). Briefly, SLS1/2 was a mission with moderate intake and no mandatory exercise requirement, with the subjects being in approximate energy balance. For Skylab, the exercise requirements were

<table>
<thead>
<tr>
<th>Table 4. Ratio of carbohydrate to fat calories in preflight and inflight diets for the SLS1/2 and LMS shuttle missions</th>
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</thead>
<tbody>
<tr>
<td>All subjects</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>SLS1/2 (m + f, n = 7)</td>
</tr>
<tr>
<td>SLS1/2 (m, n = 4)</td>
</tr>
<tr>
<td>LMS (m, n = 4)</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 vs. preflight.
considerable, but dietary input was high, so subjects were only in mildly negative energy balance (36). On LMS, the workload from the required exercise program was high, dietary intake was low, and the astronauts were in serious negative energy balance.

For the SLS1/2 astronauts, endogenous lipid mobilization was minimal because they were in approximate energy balance (41). In contrast, the LMS astronauts were in negative energy balance (~15 kcal·kg\(^{-1}\)·day\(^{-1}\)) and mobilized ~1.4 kg (~100 g/day) of body fat during spaceflight (43). If norepinephrine stimulates fat mobilization in space as it does on the ground (11, 15, 20, 24), it would be expected that norepinephrine activity would be greater among the LMS males than among the SLS1/2 males, as was found (Fig. 2). Even with this increase, catecholamine excretion was still depressed during spaceflight.

**Ratio of carbohydrate to fat in the metabolic fuel mix.** The Skylab norepinephrine data are different from those of either LMS or SLS1/2 (Fig. 2) but are consistent with our interpretation of the shuttle data. The three Skylab missions lasted 28, 56, and 84 days. Dietary intake and the amount of exercise done were increased from the 28-day mission to the 84-day mission. There was an apparent trend for the nitrogen losses to decrease with increasing energy intake (29, 37, 38).

On two of the three Skylab missions (missions 3 and 4), norepinephrine excretion was either unchanged or even increased with spaceflight (Fig. 2). Dietary intake was highest for the Skylab 4 astronauts, and they lost the least amount of protein and fat (29, 36). The implication is that they had less need to mobilize body fat; hence the lower norepinephrine excretion on Skylab 4. The energy intake deficits on Skylab missions 2 and 3 were far less than on LMS (Fig. 3), and the decrease in norepinephrine excretion was less (Fig. 2). The expected result is that the greater the energy deficit, the more norepinephrine activity to mobilize endogenous fat. Skylab 4 and SLS1/2 should be comparable, because in both cases, astronauts were in approximate energy balance, but norepinephrine excretion was greater on Skylab 4 (P < 0.05). The following explanation is suggested for these differences.

Shuttle diets are significantly higher in carbohydrates than the astronauts’ habitual diets or the diets provided to astronauts preflight (25). Table 4 gives the ratios of carbohydrate to fat in the diets of the SLS1/2 and LMS crews. Although the ratio of carbohydrate to fat intake was ~30%, greater inflight than preflight on SLS1/2, the increase was not statistically significant. The reason was that there was an outlier, who greatly increased fat intake inflight. For the other six subjects, the ratio preflight was 1.64 ± 0.09 and inflight was 2.39 ± 0.25 (P < 0.05). For this subject the ratio of carbohydrate to fat decreased from 2.56 preflight to 1.67 inflight. In a previous report, we had identified this particular individual as having an anomalous pattern of dietary intake inflight. This individual’s dietary intake remained depressed on flight day 2 (Fig. 4 in Ref. 43) and then increased steadily until the end of the mission when intake was ~50% greater than the mean preflight intake.

In the fed state, the fuel mix oxidized by the cells reflects the diet but is not wholly derived from the diet. The source of fatty acids oxidized by the tissues is a mixture of dietary and adipose tissue triglycerides because of the continuous free fatty acid-triacylglycerol cycling that occurs. As a result of fatty acid-triacylglycerol cycling, only a proportion of dietary lipids is oxidized in the period immediately after ingestion (6). Even at rest, fatty acid release exceeds oxidation about twofold (19, 23). The amount of fat oxidized depends on the regulation of lipolysis, which is subject to regulation by norepinephrine. Thus increasing the proportion of carbohydrate in the diet at the expense of fat will depress free fatty acid-triacylglycerol cycling via a decrease in norepinephrine activity. There was no carbohydrate-to-fat effect on Skylab, because the subjects were on a controlled diet before and during flight; hence the lower norepinephrine excretion on the two shuttle flights. For the shuttle missions, diet was monitored but not controlled, and for unknown reasons, all but one of the shuttle crew members selected diets low in fat.

**Sexual dimorphism.** Our analysis of the SLS1/2 norepinephrine data showed a statistically significant difference in the responses of men and women (Table 2 and Fig. 1). There were no differences in energy intake or N balance. There was a large reduction in norepinephrine excretion inflight for the men (41 ± 9% of preflight) and no change with the women (98 ± 10%, P < 0.05). Although the number of women was small (n = 3), the data showing a difference in response between men and women is statistically significant, and there was adequate power (Table 3, F = 8.45, α = 0.05, power = 0.82). The result with women was reproducible. As we have pointed out, the results were similar for the subject who flew on both SLS1 and SLS2.

Most bed rest studies where catecholamine data have been reported have been on males. An exception was the bed rest study by Blanc et al. (7), who studied men and women. A greater reduction in norepinephrine was found in males, although the reduction was not statistically significant (men 31%, women 16%).

The decreased sensitivity to norepinephrine in women is not restricted to spaceflight or fuel metabolism. Another β-adrenergic response that is attenuated in females is the response to hypoxia (2). Catecholamines control the adenylyl cyclase activity of many different types of cells by acting on β-adrenergic effectors. Modifications of norepinephrine release, synthesis, and turnover occur during head-down bed rest (17, 32) and in the stand test (18), and norepinephrine has been implicated in both the cardiovascular changes that occur during bed rest and the post-bed rest orthostatic hypotension.

There is multiple redundancy in the regulation of the pathways involved in fuel metabolism. Provision of a constant fuel supply to the tissues is effected by a mixture of the regulatory (insulin, glucagon, etc.) and counterregulatory (epinephrine, norepinephrine, corti-
sol, etc.) hormones acting in concert. In any given situation, all are active, but the relative contributions vary with fuel needs, sources of energy available, and gender. The complexity and redundancy within the system enable fast and targeted responses to be made if fuel needs change. It is obvious why there is an advantage to having different mechanisms for stress and non-stress situations, but why it should be related to gender is not known, nor whether there are any benefits therefrom. There is some evidence that the difference may relate to sex hormones. Endogenous sex steroids are involved in the regulation of catecholamine activity and can modify catecholamine release (33).

A number of explanations for the sexual dimorphism have been suggested in the literature. These are either based on the greater amount of fat in the female body or somehow linked with reproduction and lactation. A study of ovine fetal metabolism showed that the fetus uses catecholamines to mobilize the limited amount of endogenous substrates available to the fetus (31).

Three recent papers on this topic concluded that “the role played by gender in physiological responses to stress is incompletely understood” (11), and “[I]t is presently unknown whether differences in carbohydrate utilization in men and women can be explained by differences in substrate delivery, hormone action or the capacity for substrate utilization” (20). A third paper speculated that “[S]ince high sympathetic activity and low parasympathetic activity are associated with cardiovascular disease and mortality, the favorable autonomic profile seen in women may be related to their delayed onset of cardiovascular disease and increased longevity compared with men” (5).

In summary, norepinephrine excretion during spaceflight is variable. It is both mission and gender dependent. Men show the greater response, with at least three factors being involved, of which only one is due to microgravity. The dominant responses appear to be those related to fuel metabolism, specifically energy balance, and the ratio of carbohydrate to fat in the diet.

In a previous publication, we defined three criteria to distinguish between a true response to microgravity and a response to the spacecraft’s environment. Any spaceflight-specific response should 1) be apparent immediately after entry into orbit, 2) remain reasonably constant for the duration of spaceflight, and 3) apply to all of the subjects. As a result of the data reported here, we now add a fourth criterion: there should not be a simple nonspaceflight explanation for an effect observed during spaceflight.

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