Reduction of Chronic Psychosocial Hypertension in Mice by Decaffeinated Tea

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SUMMARY The effects of decaffeinated green tea on CBA mice have been contrasted with those of water during 3 to 5 months of exposure to various intensities of social stress. Intensity was modified by using different types of caging: Henry-Stephens complex population cages for maximum stress, open field population cages for intermediate levels, and siblings in standard mouse boxes for minimal stress. Two population densities were used: high, with 16 males and 16 females per population cage; and low, with approximately half this number. In three sets of experiments, 58 comparisons were made between body weight, blood pressure, pulse rate, scarring, blood urea nitrogen (BUN), adrenal and heart weights, plasma corticosterone, adult male mortality, and number of weanlings of those on decaffeinated green tea and matched groups on water. Twenty-five of the comparisons indicated less arousal with the decaffeinated green tea and in none was the water favored. Blood pressure fell from 150 to 133 mm Hg. These results support the proposal that the polyphenols (bioflavonoids) of tea may have a beneficial sedative action. (Hypertension 6: 437-444, 1984)

KEY WORDS • blood pressure • adrenal weight • bioflavonoids • plasma corticosterone • psychosocial stress

A recent authoritative review of the physiology of human essential hypertension presents strong evidence for the etiologic role of repeated arousal of the sympathetic adrenal medullary system during episodes of social interaction.\(^1\) We have long produced psychosocial hypertension in an animal model that applies this principle by using colonies of male and female mice competing for control of territory and nest establishment in Henry-Stephens complex population cages.\(^2,3\) The males develop a blood pressure of 155 to 160 ± 20 mm Hg, which is significantly higher than their normal 125 ± 12 mm Hg.\(^4\)

These animals also show early arteriosclerosis,\(^5\) and there is an increase in the catecholamine-synthesizing enzymes in the adrenals\(^6\) and in the activity of the renin-angiotensin systems.\(^7,8\) A beta-blocker, metoprolol, returns the renin and blood pressure to normal.\(^9\) However, adrenal cortical arousal with elevated plasma corticosterone persists, and a progressive, and often fatal, chronic interstitial nephritis gradually develops.\(^1\)\(^9\) The mechanism of the nephritis is not decided, but chronic reflux of urine, due to emotional difficulties in urination with ensuing sensitization to Tamm Horsfall protein, is currently being studied.\(^10\)

We have examined the effect of various agents on the hypertension developed under continuous psychosocial stress.\(^2\) Preliminary observations show no effect of a low salt diet,\(^1\) but detailed studies of the effects of caffeine show that it intensifies the hormonal and pathophysiological changes that accompany psychosocial stress.\(^11\) Even decaffeinated coffee, which contains a residual 3%, that is, 16 mg/liter of the original 560 mg/liter caffeine content of brewed coffee, has a slight potentiating effect on blood pressure and on the other effects of stress. The brewed black tea that we used contained 440 mg/liter of caffeine, or four-fifths that of our brewed coffee. Our analysis showed that it had the same effects on the colonies of competing mice as coffee.

Nevertheless, there is evidence that the physiological effects of brewed tea and coffee do differ in some respects. In 1966, Little et al.\(^12\) reported a correlation between the amount of coffee ingested and a number of serum lipid fractions in patients with coronary heart disease. To their surprise, tea had no such effect.\(^1\)\(^2\) The following year, Young et al.\(^13\) reported that rabbits given a tea supplement to an atherogenic diet had lower serum lipoproteins and less atherosclerosis than those on the diet alone. Akinyanju and Yudkin\(^14\) found that coffee enhanced the increase of blood lipids induced by an atherogenic diet; an effect that was abol-
ished by decaffeination. Tea had the opposite effect, and they commented: "Presumably, tea contains a substance that acts to decrease serum lipids more strongly than caffeine acts to increase them."14

Recently, Buda et al. (unpublished data) have shown that decaffeinated black tea has a sedative effect on the electroencephalograph of conscious cats, and Enslen and Wurzner (unpublished data) have described a modest reduction of the blood pressure of spontaneously hypertensive rats when given decaffeinated black tea. They propose that the decaffeination brings out the weak physiological effects of other substances present in tea, most likely the bioflavonoids. Since an effectively decaffeinated green tea (containing only 1.3 mg/liter) was available for research, we initiated a series of studies on the responses of mice to our psychosocial model of hypertension, while they were drinking this beverage. We followed procedures similar to those used for our studies of caffeine9 and other substances.9 We not only encountered a statistically significant lowering of blood pressure (150 to 133 mm Hg), but there were several other changes in the same direction which pointed to a sedative action and which diminished the pathophysiology induced by chronic psychosocial stress in mice.

Methods

Male mice were raised with their siblings (4 to 8) per standard mouse box (29 x 18 x 13 cm) until 4 months of age. At this point a random grouping of 16 males and 16 females, raised under the same conditions, were placed in a Henry-Stephens complex population cage (Figure 1). The cage was comprised of a hexagonal central feeding and watering box that was connected into a circle by flexible plastic tubing. The multiple entrances to the box made the defense of territory and establishment of nesting areas difficult.2 4 The narrow connecting tubes permitted one-way passage only, encouraging confrontations, and the central location of the food and water forced the competing males into proximity.4 The intense social stress that developed could be decreased by reducing population density and also by modifying the design of the population cage to an "open field," as shown in Figure 2. This permitted the mice to establish territories and to escape from one another more readily than when they were in the Henry-Stephens population cage.2 In the studies that we describe, both the above methods of reducing stress were employed.

The food in the central bin of the population cage was replenished and the four 250 cc bottles were filled with fresh beverage three times a week. The population cages were inspected daily for failing or dead mice. The cage boxes were vacuumed, and the shavings replaced once a week. Each month, the females were inspected and the males were placed in a warming box preparatory to making blood pressure measurements. The measurements were made between 1100 and 1400 hours, and the tea or water was available at all times. The backs and tails of the males were
examined for nicks and bites and epilation of fur. They were weighed, and their blood pressure and pulse rate were recorded. In this study, only the last set of measurements was used. Both experimental and control animals were measured within the same time frame.

When necessary, blood samples were drawn into Natleson blood-collecting tubes by retroorbital puncture. Blood urea nitrogen (BUN) was measured by the Azostix method upon sacrifice of the animals. Both control and experimental mice were autopsied on the same day, when they were again examined for general physical condition and scarring. The hearts, kidneys, adrenals glands, testes, seminal vesicles, and preputial glands (if necessary) were weighed on a microtorsion balance and either fixed in 10% formalin for histopathological study or frozen for biochemical assay, as in the case of the adrenals. In later studies, corticosterone assays were run on the plasma. A recent book and a current review article describe our techniques. They refer to several previous studies of the effects of the psychosocial hypertension that develops in complex population cages.

The decaffeinated green tea given in the drinking water was first made up in a stock solution containing 3 g/500 cc distilled water, and kept refrigerated at 4°C. The stock solution was made up fresh every 2 weeks from dehydrated, vacuum-sealed tea. A fresh 1:10 dilution was then placed in the drinking bottles on Monday, Wednesday, and Friday. Three sets of studies were run.

**Experiment 1**

In the first series, 16 male and 16 female 4-month-old CBA mice were placed in Henry-Stephens population cages (Figure 1); some received the decaffeinated tea and others received water. The animals were exposed to social stimulation in these cages for 3 to 5 months, to give time for the development of the effects of chronic social stress. Parallel sets of sibling males lived in standard mouse boxes under conditions of minimal competitive stress; 28 received decaffeinated green tea and 28 received water. They were studied for the same periods of time, were exposed to the same light and sound as the experimental animals, and were terminated at the same time.

A total of 57 males that had been exposed to from 3 to 5 months of stressful competition while drinking decaffeinated tea survived in the population cages, and 38 survived the social stress while drinking water. The stressed animals in the water-fed population cages served as controls to the stressed group using tea; and the minimally stressed animals on water were controls to the minimally stressed siblings on tea in the standard mouse boxes (Tables 1 and 2).

### Table 1. Experiment 1: Clinical Observations

<table>
<thead>
<tr>
<th>Mouse group</th>
<th>Blood pressure (mm Hg)</th>
<th>Pulse rate (bpm)</th>
<th>Scarring score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boxed siblings with minimal stress</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decaf tea (n = 21)</td>
<td>36.5 ± 5.2</td>
<td>125 ± 7</td>
<td>510 ± 110</td>
</tr>
<tr>
<td>Water (n = 28)</td>
<td>37.3 ± 2.1</td>
<td>130 ± 8</td>
<td>600 ± 45</td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td><em>p</em> &lt; 0.01</td>
<td><em>p</em> &lt; 0.03</td>
</tr>
<tr>
<td><strong>Population cages with high density, high stress</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decaf tea (n = 57)</td>
<td>33.2 ± 5.0</td>
<td>143 ± 18</td>
<td>557 ± 85</td>
</tr>
<tr>
<td>Water (n = 38)</td>
<td>32.4 ± 2.0</td>
<td>155 ± 16</td>
<td>538 ± 79</td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td><em>p</em> &lt; 0.001</td>
<td>NS</td>
</tr>
</tbody>
</table>

Statistical significance was determined by analysis of variance for unequal groups.

### Table 2. Experiment 1: Laboratory Tests and Autopsy Data

<table>
<thead>
<tr>
<th>Mouse group</th>
<th>Blood urea (mg%)</th>
<th>Adrenal weight (mg)</th>
<th>Heart weight (mg)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
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<td><strong>Boxed siblings with minimal stress</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decaf tea (n = 21)</td>
<td>9.4 ± 1.7</td>
<td>3.5 ± 0.4</td>
<td>152 ± 27</td>
<td>—</td>
</tr>
<tr>
<td>Water (n = 28)</td>
<td>8.2 ± 1.6</td>
<td>4.1 ± 0.4</td>
<td>148 ± 7</td>
<td>—</td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td><em>p</em> &lt; 0.01</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Population cages with high density, high stress</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decaf tea (n = 57)</td>
<td>19.1 ± 13</td>
<td>5.5 ± 0.8</td>
<td>156 ± 13</td>
<td>11% No survivors</td>
</tr>
<tr>
<td>Water (n = 38)</td>
<td>24.2 ± 14</td>
<td>5.6 ± 1.0</td>
<td>155 ± 12</td>
<td>21% No survivors</td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td><em>p</em> &lt; 0.05</td>
</tr>
</tbody>
</table>
Results

Experiment 1

Tables 1 and 2 show the results of this first study of animals at high population density and maximal psychosocial stress.

Clinical Observations

The minimally stressed siblings became significantly (3-5 g) heavier than those competing in the high density population cages. There was no significant difference between the weights of those on tea and those in matching situations on water. There was a significant difference between the blood pressures of both the sibling and population cage groups (p < 0.01 and p < 0.001), and the pulse rates of the nonstressed controls on decaffeinated tea were significantly lower than those on water (p < 0.03). Scarring was not seen in the control siblings in boxes; but among the competing males in the population cages, it was more marked in those receiving water than decaffeinated green tea (p < 0.01).

Laboratory Tests

There was the expected difference between the normal BUN of the control siblings in boxes and the elevated mean value for the chronically stressed animals in the population cages, many of which were developing renal damage. Although the values for the population cages on decaffeinated green tea were not significantly lower than those on water, decreased competition was suggested by the lesser scarring score of the group on the beverage.

Autopsy Data

Weight of the adrenal glands of both the tea and water boxed siblings was much lower than that of the two stressed groups in the population cages (p < 0.01). This was in keeping with our previous observations. No difference was found in the stressed animals in the two sets of population cages; nor was there any difference between the heart weights of the various groups in this first set of observations (Table 2).

Mortality

The mortality figures of the animals on tea and those on water in both the above group and the second group with decreased population density (to be discussed later) were pooled. Seven out of 64 (11%) of the stressed groups on decaffeinated tea died, and 10 out of 48 (21%) of those on water. The losses occurred during the latter part of the 3 to 5 months of social stress. In the majority, the cause was renal failure. Although not significant, the figures suggest a protective effect of the decaffeinated green tea. There was no pup survival in either of the highly competitive social groups comprising the first set of studies. All newborns succumbed as the females competed for them in the first hours after birth. This is usually the fate of pups born in high density, socially disorganized, population cages with drinking water.

Experiment 2

In the second study, the intensity of social interaction was decreased by reducing the population density from 16 males and 16 females to either eight or 10 of each sex per population cage. We also placed one set of animals in open field population cages, which provided more possibility for nesting and nurturing of young by the females. In this series with reduced social stress (Tables 3 and 4) 27 of 28 males survived the 3- to 5-month exposure to stress while drinking decaffeinated tea, and all 28 of those in the matched population cages receiving water survived. Twenty-three minimally stressed siblings, drinking the decaffeinated green tea, lived as groups of six to eight in the standard mouse box. Similar groups received water.

This second study followed our routine clinical observations of regular monthly weighing, evaluation of scarring, and blood pressure and pulse rate measurements. At termination, in addition to measuring the BUN level and weighing the adrenals and hearts, plasma corticosterone measurements were initiated.

Experiment 3

It was noticed that in the low density, decaffeinated tea complex population cages, pups that were born were nurtured until fully furred and ready to wean, that is, between 3 and 4 weeks of age. This did not happen in the low density, complex population cages on water. To follow this newly observed effect, a third set of observations was initiated using low density (10 males and 10 females per cage) populations in two Henry-Stephens cages, one cage on decaffeinated tea and one on water. The open field cages were similarly used; boxed sibling males (five on decaffeinated tea and six on water) served as minimally stressed controls. Thus, a total of 51 animals were observed for a further 3 months. A count of the young that were successfully nurtured until fully furred and ready to wean, that is, between 3 and 4 weeks of age was added to the routine data collection.

In all three experiments, the measurements fell into four categories:

1. Clinical observations: monthly body weight, scarring, blood pressure, and pulse rate measurements were made, but only the data obtained at the final set of observations were reported.
2. Laboratory tests: plasma corticosterone and BUN levels
3. Autopsy data: heart and adrenal weights
4. Mortality of males in the population cages and survival of pups to weaning vs their loss due to the social disorder at time of birth.

The data are expressed as arithmetical means and standard error. The significance of the differences between the minimally stressed groups on decaffeinated tea or water and the stressed groups in population cages on the two beverages was determined by analysis of variance for unequal groups and, in the case of the mortality figures, the chi-square test. Both were done as described by Sokal and Rohlf.55

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TABLE 3. Experiment 2. Clinical Observations

<table>
<thead>
<tr>
<th>Mouse group</th>
<th>Body weight (g)</th>
<th>Blood pressure (mm Hg)</th>
<th>Pulse rate (bpm)</th>
<th>Scarring score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boxed siblings with minimal stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decaf tea (n = 23)</td>
<td>34.8 ± 3.1</td>
<td>124 ± 6</td>
<td>521 ± 82</td>
<td>-</td>
</tr>
<tr>
<td>Water (n = 21)</td>
<td>35.0 ± 2.3</td>
<td>127 ± 6</td>
<td>582 ± 43</td>
<td>-</td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td>NS</td>
<td>p &lt; 0.01</td>
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<tr>
<td>Population cages with reduced density, medium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decaf tea (n = 27)</td>
<td>32.3 ± 2.6</td>
<td>140 ± 11</td>
<td>552 ± 67</td>
<td>1.7 ± 1.0</td>
</tr>
<tr>
<td>Water (n = 28)</td>
<td>34.3 ± 1.9</td>
<td>157 ± 10</td>
<td>570 ± 82</td>
<td>2.4 ± 1.4</td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td>p &lt; 0.02</td>
<td>NS</td>
<td>p &lt; 0.01</td>
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</table>

Experiment 2

The data from the above series of studies indicated that the decaffeinated green tea gave some protection. It was thought that the population density might affect the results, and a further series was run with a reduced population to see if a clear-cut differentiation would emerge. The results of this second experiment are presented in Tables 3 and 4.

Clinical Observations

In this study there was less difference between the weights of the two groups of nonstressed animals and the two stressed groups in the population cages: 1.6 gm for the second study vs 4.1 gm for the first experiment. This is probably the result of less severe fighting and chronic arousal when using the lower population density. The blood pressure of the boxed siblings drinking decaffeinated tea did not differ significantly from those on water. Although both were at normal levels, those on decaffeinated tea had a blood pressure of 124 mm Hg, whereas those on water had a slightly higher level, 127 mm Hg. There was a significant difference between systolic blood pressures of the stressed animals on decaffeinated tea (140 ± 11 mm Hg) and those on water (157 ± 10 mm Hg, p < 0.02). As in the first experiment, the pulse rate of the minimally stressed, boxed siblings on decaffeinated tea was significantly lower than that of the group on water (p < 0.01). This difference did not extend to the groups undergoing stress in the population cages. The same significant difference between the scarring scores of the animals in the reduced density population cages was found as in the first set of experiments with a higher density (p < 0.01). This was an expression of the same trend of less intense competition among the animals receiving the decaffeinated green tea.

Laboratory Tests

There was again the expected normal BUN in the two sets of boxed siblings with the minimum stress. As in Experiment 1, the BUN of the groups undergoing stress in the reduced density population cages and receiving decaffeinated green tea was less, although it was not significant, than that of the stressed group on water, 17.2 ± 8.8 vs 22.5 ± 15 mg%. The raised values in the stress population cages were due to the development of renal failure after several months of chronic competition, with dominant-subordinate confrontations causing difficulties in urination. Data on the plasma corticosterone values were collected in the second series. The differences between the mean for the minimal stress group, 5.4 µg%, and that for those in the population cages, 8.2 µg%, was highly significant. This was in keeping with our previous experience. In neither group were the values for the animals on tea lower than those on water.

TABLE 4. Experiment 2. Laboratory Tests and Autopsy Data

<table>
<thead>
<tr>
<th>Mouse group</th>
<th>Blood urea nitrogen (mg%)</th>
<th>Adrenal weight (mg)</th>
<th>Heart weight (mg)</th>
<th>Plasma corticosterone (µg%)</th>
<th>Birth of weanlings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boxed siblings with minimal stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decaf tea (n = 23)</td>
<td>10.0 ± 3.3</td>
<td>3.8 ± 0.4</td>
<td>143 ± 10</td>
<td>5.1 ± 2.6</td>
<td>-</td>
</tr>
<tr>
<td>Water (n = 21)</td>
<td>10.5 ± 1.5</td>
<td>4.4 ± 0.5</td>
<td>156 ± 11</td>
<td>5.6 ± 3.1</td>
<td>-</td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>NS</td>
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<tr>
<td>Population cage with reduced density, medium</td>
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<tr>
<td>stress</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Decaf tea (n = 27)</td>
<td>17.2 ± 8.8</td>
<td>6.0 ± 0.7</td>
<td>159 ± 14</td>
<td>8.0 ± 3.9</td>
<td>Many</td>
</tr>
<tr>
<td>Water (n = 28)</td>
<td>22.5 ± 15</td>
<td>6.4 ± 1.1</td>
<td>165 ± 15</td>
<td>8.4 ± 4.4</td>
<td>Few</td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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</tr>
</tbody>
</table>
Table 5. Experiment 3: Clinical Observations

<table>
<thead>
<tr>
<th>Mouse group</th>
<th>Body weight (g)</th>
<th>Blood pressure (mm Hg)</th>
<th>Pulse rate (bpm)</th>
<th>Scarring score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boxed siblings with minimal stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decaf tea (n = 5)</td>
<td>38.5 ± 2.6</td>
<td>122.0 ± 4.5</td>
<td>464 ± 22</td>
<td>-</td>
</tr>
<tr>
<td>Water (n = 6)</td>
<td>34.7 ± 1.7</td>
<td>128.3 ± 6.1</td>
<td>540 ± 54</td>
<td>-</td>
</tr>
<tr>
<td>Significance</td>
<td>p &lt; 0.05</td>
<td>NS</td>
<td>p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Open field with low population density</td>
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</tr>
<tr>
<td>Decaf tea (n = 10)</td>
<td>32.7 ± 2.1</td>
<td>126.5 ± 11.8</td>
<td>440 ± 86</td>
<td>0.7 ± 0.8</td>
</tr>
<tr>
<td>Water (n = 9)</td>
<td>32.7 ± 1.4</td>
<td>142.8 ± 8.7</td>
<td>526 ± 58</td>
<td>1.0 ± 0.6</td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Henry-Stephens population with low density</td>
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<td></td>
</tr>
<tr>
<td>Decaf tea (n = 9)</td>
<td>34.4 ± 1.1</td>
<td>133.9 ± 7.8</td>
<td>533 ± 97</td>
<td>1.4 ± 0.7</td>
</tr>
<tr>
<td>Water (n = 10)</td>
<td>33.0 ± 1.5</td>
<td>147.0 ± 9.2</td>
<td>624 ± 65</td>
<td>2.4 ± 0.7</td>
</tr>
</tbody>
</table>

Autopsy Data

Although the corticosterone levels of the two groups did not differ for the tea and water groups, the mean adrenal weights of the minimum stress siblings in boxes were significantly lower in those receiving decaffeinated green tea than in those on water (p < 0.01). The mean adrenal weight of the stressed animals on tea was 7.0 ± 0.7 mg as opposed to 6.4 ± 1.1 mg for those on water. This difference deviated in favor of the animals on water, but did not reach significance. The heart weights of the siblings on tea were significantly less than those on water (p < 0.01), and the values for the stressed groups were 159 ± 14 mg for tea and 165 ± 15 mg for water, which suggests that tea is protective.

Mortality

Only the pups will be considered, since the pooled data for the adults have been discussed above. The stressed animals drinking tea produced many healthy, fully furred weanlings per population cage while those on water produced only a few. This was further evidence that the decaffeinated green tea had some effect in reducing the agitation and mutual stimulation of the psychosocially stressed groups.

Experiment 3

Tables 5 and 6 show the results of the third set of observations in which plasma corticosterone measurements were routinely used and the precise number of fully furred weanlings was now recorded.
Clinical Observations

The body weight of the boxed sibling controls with minimal stress and drinking decaffeinated green tea was significantly heavier than that of the boxed siblings on water, 38.5 vs 34.7 (p < 0.05), respectively. Although the tea animals were heavier, the differences between the open field cages and between the low density Henry-Stephens population cages were not significant. The blood pressure of the tea groups in both sets of population cages was approximately 15 mm Hg lower (p < 0.01) than that of those on water. The scarring scores, a measure of the amount of fighting, were consistent with this result; there were no scores in the boxed siblings, minimal ones in the open field, with fewer in the tea than water open field mice, and significantly lower scores in the tea Henry-Stephens population cage, that is, 1.4 vs 2.4 (p < 0.01).

Laboratory Tests

The data in this new series reflected the diminished social stress in the open field and complex population cages due to the lower population density. The BUN was normal (10 mg%) in the two sets of boxed siblings; but in the tea open field, it was significantly lower (10.5 mg%) than that for water (18.5 mg%). The complex population cages yielded very similar data (p < 0.05). The mean plasma corticosterone levels of the tea animals were consistently lower than those on water; the difference attained significance in the complex population cages, 4.5 vs 10.5 μg% (p < 0.05).

Autopsy Data

The adrenal weights were consistently lower in the groups on decaffeinated green tea: the difference attained significance for boxed siblings (p < 0.01) and complex population cages (p < 0.05) but not for the open field group. Heart weights were significantly lower (p < 0.05) in the complex population cages where the tea animals competed less vigorously. This was supported by the lower blood pressure levels and scarring scores.

Male Mortality and Survival of Pups

In this third study, one male (10%) died in the tea open field group, and one died in the water complex population cage group. This contrasts with 20% in the high-stress, high-density, population cages. More than twice the number of pups grew up successfully in the open field population cage with low density and drinking tea than in the water open field, 84 vs 39, respectively. This is supported by the results of the complex population cages. There were no pup survivors in the group on water, but the tea group produced 36 weanlings.

Discussion

In three separate studies, a total of 58 comparisons contrasted the effect of decaffeinated green tea, which contained only traces of caffeine (1.3 mg/liter), with the effect of decaffeinated coffee (caffeine, 16 mg/liter) and of water on boxed siblings and on animals competing in two different styles of population cages. In 25 cases, there was a statistically significant bias favoring the tea. These changes were found in boxed siblings experiencing minimal stress as well as in those competing in the various population cages at varying levels of stress. Even the changes in the minimal stress siblings, such as lower adrenal weights and normal blood pressure, were those to be expected if the animals were more relaxed when taking the decaffeinated tea.

The tea appears to affect central regulatory mechanisms and thereby to influence the neuroendocrine system. Since the blood pressure and pulse rate were affected, the sympathetic adrenal medullary system may be involved. And since there were only minor changes in adrenal weight and plasma corticosterone, the pituitary-adrenal cortical system may not be so much affected. The changes were persistent, and habitation did not occur despite several months' use of the decaffeinated green tea. The lifespan of a mouse is approximately one-thirtieth that of humans, and the duration of this study was the equivalent of 10 to 15 of our years. Not only were there measurable clinical and endocrine differences, but also the mortality of the adults was reduced and parental care was more effective.

The tea plant, which relates to the old Linnaean genus, camilla, has leaves that contain large amounts of bioflavonoids. From 17% to 30% of the dry weight of the fresh tea leaf is composed of these polyphenols. The predominant bioflavonoids in tea are the so-called flavanols, epicatechin and epicatechin gallate, with higher percentages present in the better teas. Although their amount is much decreased as a result of the enzyme action during the fermentation that converts green to black tea, their structure is such that they can be expected to remain stable in the stock solutions that we held at 4°C, in the dark, for 2 weeks.

It is established that some bioflavonoids (there are over 800 recognized compounds) inhibit the catechol-O-methyltransferase (COMT) responsible for the further metabolism of catecholamines. On the other hand, Andary's excellent study of the bioflavonoids of the parasitic plant, orobanche, indicates the reverse effect, namely, that some flavonoids can activate COMT, thereby perhaps decreasing levels of catecholamines. Recognizing that other bioflavonoids have the opposite effect, he comments that their action depends on their precise molecular structure. Using the bioflavonoids, verbascoside and orobanchoside, in rats, he demonstrated a significant antihypertensive effect sustained during weeks of oral administration. As a result of separate experiments studying this point, he concluded that it could be due to a beta-blocking action of the bioflavonoids.

Certain bioflavonoids affect the pituitary-adrenal axis and cause mild thymic involution. They also protect ascorbic acid against oxidation. The resemblance of the bioflavonoid molecule to estrone has been related to their hypocholesterolemic action. In their comprehensive review of the pharmacological
aspects of tea, Das et al.²⁴ cite the work of the Russian Kursanova who in the 1950s reported that green tea bioflavonoids have beneficial effects on hyperthyroidism.

It is known that the bean, cicer arietinum (Bengal gram), the staple diet of the people of low socioeconomic status in Northern India, leads to low levels of serum cholesterol. This has been shown in experiments on rats²⁵ and long-term feeding studies in humans.²⁶ Recently, Siddiqui and Siddiqui²⁷ showed that the bean contains the bioflavonoids biochanin-A and formononetin, which reduced the serum cholesterol of rats that had been made hyperlipidemic by a combination of diet and injections of Triton WR 1339.

In an ingenious recent study, Rouse et al.²⁸ compared the blood pressure of vegetarian Seventh-Day Adventists with omnivorous Mormons. Since both groups avoid caffeine, tobacco, and alcohol, and since their belief and principles are similar, diet was the major difference between them. Rouse et al. found that the systolic blood pressure of both male and female vegetarians was significantly (5–6 mm Hg) lower than that of the omnivores. In a further well-controlled experiment, the diet was given to healthy omnivorous subjects in a crossover design,²⁹ and the same 5–6 mm Hg fall was observed. The cause was not determined, but changes in sodium or potassium intake did not appear to be involved.

The blood pressure of low socioeconomic status villagers in Northern India was low in the 1950s, when cicer arietinum was a dietary staple.³⁰ It is a testable hypothesis that the effects observed by Rouse et al. may have been due to the greater flavonoid content of the vegetarian diet.

The above evidence suggests that bioflavonoids can significantly change the regulation of plasma cholesterol³¹ and blood pressure³² by their effects on the brain and neuroendocrine system.

Acknowledgments

Part of this work was carried out at the Human Centrifuge Laboratory of the University of Southern California, Los Angeles, California, and part at the Animal Research Facility, Veterans Administration Hospital, Loma Linda, California. We thank Dr. Jordan L. Cohen, School of Pharmacy, University of Southern California, for the caffeine assay. We also wish to thank Nestle Products, Technical Assistance Company, Ltd., LaTour de Peitz, Switzerland, for financial support and for providing decaffeinated green tea.

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Hypertension. 1984;6:437-444
doi: 10.1161/01.HYP.6.3.437

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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