Coca chewing for exercise: hormonal and metabolic responses of nonhabitual chewers

ROLAND FAVIER, ESPERANZA CACERES, LAURENT GUILLON, BRIGITTE SEMPORE, MICHEL SAUVAIN, HARRY KOUBI, AND HILDE SPIELVOGEL
Instituto Boliviano de Biología de Altura, Casilla 717, La Paz; Institut Français de Recherche Scientifique pour le Développement en Coopération (ORSTOM), Casilla 9214, La Paz, Bolivia; and Unité de la Recherche Associée 1341 Centre National de la Recherche Scientifique, Laboratoire de Physiologie, Université Claude Bernard, 69373 Lyon cedex 08, France

Favier, Roland, Esperanza Caceres, Laurent Guillón, Brigitte Sempore, Michel Sauvain, Harry Koubi, and Hilde Spielvogel. Coca chewing for exercise: hormonal and metabolic responses of nonhabitual chewers. J. Appl. Physiol. 81(5): 1901–1907, 1996.—To determine the effects of acute coca use on the hormonal and metabolic responses to exercise, 12 healthy nonhabitual coca users were submitted twice to steady-state exercise (~75% maximal O2 uptake). On one occasion, they were asked to chew 15 g of coca leaves 1 h before exercise, whereas on the other occasion, exercise was performed after 1 h of chewing a sugar-free chewing gum. Plasma epinephrine, norepinephrine, insulin, glucagon, and metabolites (glucose, lactate, glycerol, and free fatty acids) were determined at rest before and after coca chewing and during the 5th, 15th, 30th, and 60th min of exercise. Simultaneously to these determinations, cardiorespiratory variables (heart rate, mean arterial blood pressure, oxygen uptake, and respiratory gas exchange ratio) were also measured. At rest, coca chewing had no effect on plasma hormonal and metabolic levels except for a significantly reduced insulin concentration. During exercise, the oxygen uptake, heart rate, and respiratory gas exchange ratio were significantly increased in the coca-chewing trial compared with the control (gum-chewing) test. The exercise-induced drop in plasma glucose and insulin was prevented by prior coca chewing. These results contrast with previous data obtained in chronic coca users who display during prolonged submaximal exercise an exaggerated plasma sympathetic response, an enhanced availability and utilization of fat, and a lower respiratory exchange ratio. We conclude that, whereas coca chewing might affect glucose homeostasis during exercise, none of the physiological data provided by this study would suggest that acute coca chewing in nonhabitual users could enhance tolerance to exercise.

fat metabolism; glucoregulatory hormones; submaximal exercise; sympathoadrenal activation

Coca has been an integral part of the cultural life of Bolivia and Peru since pre-Incaic times (5, 6). Various segments of the indigenous population chew it to cure a variety of ailments, and it is highly praised for preventing fatigue during work at altitude (12). Indeed, the proportion of Indians chewing coca increases with altitude, and Monge (20) claimed that coca leaf was, in some unknown manner, indispensable for long-term adaptation to the high altitudes where many Aymara and Quechua Indians live.

Recently, Spielvogel et al. and Favier et al. examined the effects of coca chewing on maximal (22) and submaximal (11), respectively, exercise response in traditional coca users (agriculturalists). In those studies, they found that maximal aerobic capacity [maximal O2 uptake (VO2peak)] and work efficiency (η) were similar in chewers and nonchewers (22) but that coca chewing increased plasma epinephrine (Epi) concentration, enhanced plasma free fatty acid (FFA) availability, and lowered the respiratory exchange ratio (RER) during prolonged submaximal exercise (11). In the previous studies (11, 22), the protocol design did not allow a delineation as to whether the metabolic adaptations reported in coca users were linked to acute or chronic effects of coca absorption. Because coca chewing before exercise causes an elevation in plasma Epi and may enhance fat metabolism (11), we hypothesized that the metabolic and hormonal effects observed in chronic coca users were possibly linked to cellular adaptations that have facilitated fat oxidation.

To clarify the issue of acute vs. chronic effects of coca chewing, the present study examined the major metabolic and hormonal effects of acute coca chewing by nonhabitual coca users. The major glucoregulatory hormonal (catecholamines, insulin, and glucagon) and metabolic responses to a single absorption of coca were examined during prolonged submaximal exercise, and the results were compared with those obtained in the same subjects without coca chewing.

MATERIAL AND METHODS

Subjects. Twelve students volunteered to participate in the study. On the basis of a questionnaire, all of these subjects were considered as nonchewers. Even though we have no objective proof of their lack of habituation in coca chewing, we believe that they were nonhabitual users (see Discussion). The experimental procedures and potential risks of the study were explained to each subject both verbally and in writing. All subjects gave informed consent, and the experiment was approved by the local Ethics Committee (Universidad Mayor San Andres, La Paz, Bolivia). All subjects were physically active, but none was involved in a training program. They were asked to maintain their usual activity throughout the study. Body mass and height were measured with a standard scale and an anthropometer, respectively. Skinfolds (biceps, triceps, subscapular, and suprailiac) were measured with a caliper (Holtain), and body composition was estimated from percent body fat calculated from skinfolds and body weight (10). The pertinent characteristics of the subjects are summarized in Table 1. All measurements were performed at the Instituto Boliviano de Biología de Altura (La Paz, Bolivia; mean altitude 3,600 m).

Procedure. Before the experimental trials, all subjects underwent, on a mechanical bicycle, an incremental exercise test that permitted VO2peak determination. This test was...
Conducted to select an appropriate work rate for the subsequent trials. Before all tests, the subjects were asked to abstain from vigorous exercise for 24 h and reported to the laboratory after fasting overnight. The procedure for each test was identical, including the insertion of a catheter into an antecubital vein 70 min before exercise. After a 10-min supine rest (R1), the subjects remained seated on a chair for a 60-min period during which they were asked to chew either a sugar-free chewing gum (Coca-1) or 15 g of coca leaves (Coca-2). The coca leaves contain 0.4-0.7% of cocaine (M. Sauvain, unpublished data). All subjects performed both trials 1 mo apart, and the order of the Coca- and Coca-2 trials was randomized.

After a 10-min rest on the bicycle (R2), the subjects exercised for 60 min at a power output designed to elicit ~75% VO2peak. Identical weights were placed on the pan exercised for 60 min at a power output designed to elicit a steady-state oxygen uptake (Tissot spirometer) and for O2 and CO2 (Servomex ear-clip attachment). By use of a cuff around the arm, systolic blood pressure was measured with an ear oximeter (Ohmeda, Biox 3000). The SaO2 was measured continuously by bipo-

Table 1. Summary of characteristics of subjects

| Age, yr | 27.1 ± 1.6 (19.0–45.1) |
| Body weight, kg | 65.6 ± 1.7 (57.0–78.0) |
| Height, cm | 169 ± 1.7 (161–181) |
| Body mass, W | 185 ± 8 (135–261) |
| HRmax, beats/min | 184 ± 3 (161–200) |
| VO2peak, liters O2/min | 5.70 ± 0.52 (4.67–6.78) |
| VO2peak, ml O2·kg−1·min−1 | 39.4 ± 6.0 (33.1–46.8) |

Values are means ± SE; nos. in parentheses, range. Wmax, maximal power output; HRmax, maximal heart rate; VO2peak, peak O2 uptake.

Table 2. Plasma hormones and metabolites at rest

<table>
<thead>
<tr>
<th></th>
<th>Coca</th>
<th>Coca-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>R2</td>
<td>R1</td>
</tr>
<tr>
<td>Epi, pg/ml</td>
<td>149 ± 14</td>
<td>150 ± 18</td>
</tr>
<tr>
<td>NE, pg/ml</td>
<td>314 ± 52</td>
<td>447 ± 41</td>
</tr>
<tr>
<td>Insulin, μU/ml</td>
<td>15.7 ± 2.3</td>
<td>20.3 ± 2.7</td>
</tr>
<tr>
<td>Glucagon, pg/ml</td>
<td>179 ± 19</td>
<td>181 ± 0</td>
</tr>
<tr>
<td>Glucose, mM</td>
<td>5.03 ± 0.25</td>
<td>5.57 ± 0.33</td>
</tr>
<tr>
<td>FFAs, mM</td>
<td>0.193 ± 0.038</td>
<td>0.181 ± 0.028</td>
</tr>
<tr>
<td>Glycerol, mM</td>
<td>0.132 ± 0.007</td>
<td>0.132 ± 0.010</td>
</tr>
</tbody>
</table>

Values are means ± SE. Coca-2, chewing group chewing sugar-free chewing gum; Coca-1, chewing group chewing 15 g of coca leaves; R1, blood sampling in supine position 10 min after catheter implantation; R2, blood sampling in sitting position on bicycle after 1 h of chewing; Epi, epi-nephrine; NE, norepinephrine; FFA, free fatty acids. *Significantly different from Coca-1. †Significantly different from R1.

Statistical analysis. Statistical comparisons between groups were calculated with two-way analysis of variance with repeated measures (STATVIEW 4.02, Abacus Concepts, Berkeley, CA). Fisher’s protected least significant difference for multiple comparisons was used post hoc when significant F ratios were obtained. The level of significance was set at 5%.

RESULTS

Effects of coca chewing on hormonal and metabolic status at rest (Tables 2 and 3). The plasma concentration of glucoregulatory hormones and metabolites was similar in both trials at R1 (i.e., in supine position before chewing; Table 2). In both conditions (Coca-1 and Coca-2), there was a significant increase in plasma NE from R1 to R2, whereas plasma Epi remained stable. On the other hand, plasma insulin tended to increase from R1 to R2 in control conditions (Coca-2), whereas it decreased significantly subsequently to coca chewing. Glucagon, glucose, and FFAs were similar in both trials whether before (R1) or after (R2) chewing.

The cardiorespiratory variables measured at rest (R2) were similar in both trials (Table 3).

Effects of prior coca chewing on the hormonal and metabolic responses to submaximal exercise. The absolute and relative work intensities during exercise were identical in the Coca-1 and Coca-2 trials (Table 4).

Table 3. Cardiorespiratory variables measured at R2

<table>
<thead>
<tr>
<th></th>
<th>Coca</th>
<th>Coca-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2, ml·kg−1·min−1</td>
<td>4.9 ± 0.4</td>
<td>5.2 ± 0.3</td>
</tr>
<tr>
<td>VCO2, ml·kg−1·min−1</td>
<td>4.5 ± 0.4</td>
<td>5.0 ± 0.4</td>
</tr>
<tr>
<td>RER</td>
<td>0.92 ± 0.02</td>
<td>0.96 ± 0.04</td>
</tr>
<tr>
<td>Ve, l/min</td>
<td>12.8 ± 10</td>
<td>14.8 ± 1.8</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>78 ± 3</td>
<td>76 ± 4</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>94 ± 1.6</td>
<td>94.5 ± 0.4</td>
</tr>
<tr>
<td>MABP, mmHg</td>
<td>89 ± 2</td>
<td>93 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE. VO2, O2 uptake; VCO2, CO2 production; RER, respiratory exchange ratio; Ve, ventilatory output; HR, heart rate; SaO2, arterial O2 saturation; MABP, mean arterial blood pressure.
During prolonged exercise, there was a significant effect of coca chewing on $\dot{V}O_2$, $\dot{CO}_2$ production, RER, and HR, which were all significantly increased in the Coca\textsuperscript{1} trial (Figs. 1 and 2). Neither SaO\textsubscript{2} nor MABP was affected by coca chewing.

The exercise-induced responses of the glucoregulatory hormones are reported in Fig. 3. It appeared that the sympathoadrenergic activation was similar in both trials. By contrast, the exercise-induced drop in plasma insulin was significantly reduced subsequent to coca chewing, whereas plasma glucagon tended to be higher during the last 0.5 h of exercise after coca chewing (Fig. 3).

The plasma metabolic levels during prolonged submaximal exercise are reported in Fig. 4. During the first 0.5 h of exercise, plasma glucose dropped significantly in the Coca\textsuperscript{1} trial but remained rather stable after coca chewing. On the other hand, the exercise-induced plasma lactate accumulation was similar in the two trials. With respect to fat metabolism, it appeared that both lipolysis (as assessed by glycerol concentration) and FFA availability were superimposable in the Coca\textsuperscript{1} and Coca\textsuperscript{2} trials.

**DISCUSSION**

In a series of recent reports, Bracken and colleagues (2, 3) and Conlee et al. (7) examined in rats the combined physiological effects of cocaine and exercise. Their results have shown that cocaine treatment during exercise causes an exaggerated catecholamine response (3, 7), an accelerated rate of glycogen depletion (2), a rapid accumulation of blood lactate response (2), and reduced endurance (2). Recently, Favier et al. (11)
and Spielvogel et al. (22) examined the effect of coca chewing on the hormonal and metabolic responses to exercise in chronic coca users (agriculturalists). Favier et al. (11) found that, at rest, coca chewing during a 1-h period was followed by a significant increase in blood glucose, FFAs, and NE concentration and a significant reduction in plasma insulin level. In addition, during prolonged submaximal exercise, coca users were found to display a significantly greater adrenal activation (as assessed by a higher level of plasma Epi) and an increased use of fat (as evidenced by a lower RER). In those studies (11, 22), physiological data were collected in traditional coca users after acute coca chewing, and the results were compared with those of nonchewers. However, because of the experimental protocol design, they felt in retrospect that the observations could be linked either to acute effects of coca chewing or to some physiological adaptations consecutive to chronic coca use. To clarify this issue, in the present study, we examined the physiological response to exercise in a

![Figure 3](image1)

**Fig. 3.** Hormone exercise-induced changes ($\Delta = \text{values at } X \text{ (time)} - \text{values at rest after chewing}$) of plasma epinephrine (Epi; A), insulin (B), plasma norepinephrine (NE; C), and glucagon (D) during prolonged submaximal exercise in subjects cycling after 1 h of Coca $^-$ (○) or Coca $^+$ (■). Values are means ± SE. *Significantly different from Coca $^-$ at the same time.

![Figure 4](image2)

**Fig. 4.** Metabolite exercise-induced changes ($\Delta = \text{values at } X \text{ (time)} - \text{values at rest after chewing}$) of glucose (A), lactate (B), free fatty acids (C), and glycerol (D) during prolonged submaximal exercise in subjects cycling after 1 h of Coca $^-$ (○) or Coca $^+$ (■). Values are means ± SE.
group of nonhabitual coca users with (Coca\textsuperscript{−}) and without (Coca\textsuperscript{+}) prior coca chewing. We did not have any certainty about a lack of habituation in coca chewing in our subjects. However, in a large screening of a Bolivian population, Carter and Mamaní (6) have reported that both the prevalence of coca chewing and the amount of leaves used are clearly dependent on the standard of education. Thus coca-chewing prevalence reaches 70–75% in subjects with a low-educational background but averages only 20% in subjects with a high-educational background. In addition, the amount of coca leaves used is eight times higher in low-educational background compared with high-educational background subjects. Because most of our subjects were medical students, we believe that they can be considered as nonhabitual coca chewers and differed significantly from chronic coca users (11, 22).

The amount of coca leaves (15 g) that the subjects had to chew was chosen on the basis of previous experiments (11, 22) where it was found that the free mean use of coca averaged 16 g. On the other hand, it was shown that coca chewing results immediately in a detectable amount of cocaine in blood, which reaches peak concentration at ~1 h and persists in the plasma for several hours (13).

The results obtained in the present study showed that most of the coca-induced effects observed in traditional coca users (11) were absent in nonhabitual chewers.

Effects of coca chewing at rest. In the resting supine position (R1), the hormonal and metabolic status of the subjects was identical in both trials (Table 2). The plasma hormonal and metabolic levels remained unaltered by acute chewing of 15 g of coca leaves except for a significant increase in plasma NE (Table 2). However, a similar sympathetic activation was observed in the control conditions (Coca\textsuperscript{−}). It is likely that the significant increase in plasma NE from R1 to R2 in both trials was due to postural changes. Indeed, at R1, blood was withdrawn with the subjects in the supine position, whereas at R2, blood was collected while the subjects were sitting on the bicycle, and such postural changes have been shown to result in an increased NE concentration (8). Thus it appeared that only chronic coca use was accompanied by NE increase (11), whereas acute coca chewing was not (Table 2). The difference observed between acute and chronic coca exposure was not linked to the amount of coca leaves used (see above) but could be due to a low cocaine level in the blood and/or to the fact that cocaine may not have peaked by 1 h. However, Holmstedt et al. (13) have shown that the absorption half-life of cocaine ranged from 0.2 to 0.6 h in habitual and nonhabitual coca users. Unfortunately, we did not determine blood cocaine level but, in response to coca chewing, some changes in hormonal status (e.g., insulin, see below) were quantitatively similar in nonhabitual and chronic coca users (11), suggesting that the circulating level of cocaine should have been rather comparable in both groups of subjects. It is also possible that chronic coca use could have resulted in changes in β-adrenoreceptor number and/or sensitivity as previously reported with cocaine exposure (21). In fact, the present results reported for coca chewing are rather similar to those observed with acute exposure to hypoxia, whereas plasma NE increased significantly with chronic hypoxia (18). The absence of effect of acute coca chewing in altering circulating NE level would readily explain the unchanged plasma FFA level (Table 2).

It remains, however, that, at rest, there was a significant effect of coca chewing on circulating insulin that was significantly reduced in the Coca\textsuperscript{−} trial, whereas it tended to increase in the Coca\textsuperscript{+} trial (Table 2). This result is rather consistent with the depressed plasma insulin level observed in chronic coca chewers (11). The results of the present study indicate that circulating Epi and NE (Table 2) are not responsible for the decrease in insulin, and it seems reasonable to suggest that sympathetic neural influences to the pancreas are involved in the inhibition of insulin release after coca chewing (Table 2; Ref. 14). On the other hand, it is well known that cocaine has profound effects on the cardiovascular system, including increased HR, MABP, and total peripheral resistance (25). The widespread use of coca leaves in an Andean population warrants the collection of data to determine whether coca chewing alters cardiovascular function. From the present results (Table 3), it appeared that neither HR nor MABP was altered after coca chewing. These data contrast with those obtained in horses by McKeever et al. (19) after an intravenous administration of 0.4–0.5 mg/kg of cocaine. It is likely that, in the present study, the blood cocaine level was low. Indeed, it was reported that intravenous administration of only 0.1 mg/kg of cocaine did not result in cardiovascular alterations (19).

Effects of prior coca chewing on the subsequent physiological response to submaximal exercise. It has been previously reported that cocaine treatment before exercise causes an exaggerated catecholamine response in a dose-related fashion (3). Thus, at low doses of intraperitoneal cocaine administration (up to 0.5 mg/kg), plasma Epi and NE levels remained unaltered, whereas at doses from 2.5 to 20 mg/kg, plasma NE was higher than in control conditions, leading to an accelerated rate of glycogenolysis and early fatigue (3, 7). With coca chewing, Favier et al. (11) recently found a higher plasma Epi level during prolonged submaximal exercise and an enhanced utilization of fat. In contrast, in the present study, the exercise-induced sympathoadrenal activation was similar with and without coca chewing (Fig. 3). These results are rather consistent with recent data obtained by Kelly et al. (15), who reported that the sympathoadrenergic response to a cocaine challenge was lower in acute-coca than in cocaine-conditioned rats. The reason for a catecholaminergic sensitization to coca chewing remains to be determined, but cocaine sensitization in other behavioral responses has been previously reported (see e.g., Ref. 23). Interestingly, Vrana et al. (24) have reported that chronic cocaine
Coca substrate utilization is under sympathetic control. Only observed with prolonged use of coca (11), it can metabolism. Because we have no data on tyrosine hydroxylase activity in response to coca chewing, this issue will have to await further investigation. Nevertheless, the plasma insulin and glucagon kinetics during exercise were affected by coca chewing in a similar way in nonhabitual coca chewers (Fig. 3) and in chronic coca users (11). Collectively, the data suggest that, at a low dose of coca use (~15 g), the sympathoadrenergic responsiveness is increased only with chronic exposure to coca chewing (11), whereas the plasma level of pancreatic hormones is affected both in acute (this study) and chronic (11) conditions. By examining the plasma glucose kinetics during exercise, it appeared that coca chewing could have prevented the drop of plasma glucose that occurred in control conditions in the early phase of submaximal exercise (Fig. 4). It can be hypothesized that coca chewing resulted in a reduced peripheral glucose uptake during exercise. Indeed, plasma insulin was significantly lower in the Coca + trial (11.8 ± 1.1 and 18.8 ± 2.4 µU/ml during the 5th min of exercise for the Coca + and Coca - trials, respectively), and it was shown that insulin and exercise act synergistically to enhance glucose disposal in humans (9). It is also possible that the ability of coca chewing to prevent a blood glucose drop while the subjects were exercising was partly linked to the higher glucagon level (Fig. 3) observed during the Coca + trial. The causal relationship between glucose homeostasis and coca chewing remains, however, to be explored in greater detail. The fact that coca chewing is causally related to patterns of glucose metabolism was already noticed by Bolton (1), who reported that “chewing coca in the absence of eating raises glucose levels, especially when they may be depleted due to strenuous physical labor.”

In the previous study by Favier et al. (11), they noted that, in chronic coca users, coca chewing led to an enhanced availability and utilization of fat. In the present study, both FFA level and fat utilization (as assessed by changes in the RER) were similar in the Coca + and Coca - trials in nonhabitual coca chewers. As previously mentioned, the amount of coca leaves consumed by the subjects was similar in chronic and acute coca chewers, casting some doubt on a different cocaine absorption between present and previous studies (11, 22). It is possible that either the amount of coca leaves to be chewed needs to be larger or only repeated coca chewing is followed by a substantial alteration in fat metabolism. Because sympathoadrenergic activation is only observed with prolonged use of coca (11), it can thus be hypothesized that the coca-induced shift in substrate utilization is under sympathetic control.

In addition, we observed that the rate of VO2 during exercise was clearly affected by coca chewing (Fig. 1), the VO2 being higher in the Coca + compared with the Coca - trial, suggesting a decrease in f1. These data contrast with the unchanged f1 observed in chronic coca chewers (22) but are consistent with recent data obtained by Brutsaert et al. (4) in nonhabitual chewers. It can thus be concluded that f1 is altered by acute coca chewing, a phenomenon that vanishes when coca use is prolonged over years (11).

Finally, it was previously reported that acute cocaine administration resulted in an increased blood lactate accumulation during exercise in both rats (7) and horses (19). The present results showed that venous blood lactate concentrations were superimposable in both the Coca + and Coca - trials (Fig. 4), in agreement with previous data obtained in nonhabitual (4) and chronic (11) coca chewers. Therefore, it seems that coca chewing is not responsible for an enhancement in anaerobic metabolism.

In summary, we found that acute coca chewing in nonhabitual coca chewers increased VO2 and HR during prolonged submaximal exercise but had no effect on sympathoadrenal activity at rest and during exercise. The attenuated fall in insulin during exercise after coca chewing may suggest that this could prevent the drop in blood glucose during the early phase of exercise. Nevertheless, none of the physiological data provided by this study would suggest that acute coca chewing in nonhabitual users could enhance a tolerance for exercise.

We express our profound gratitude to the subjects without whose dedication, cooperation, and spirit this work could not have been completed. We are grateful to John Carew for help in preparing the English version of the manuscript. This study was partly supported by a grant from Ministère des Affaires Étrangères (France).Address for reprint requests: R. Favier, URA 1341 CNRS, Laboratoire de Physiologie, 8, Ave. Rockefeller, 69373 Lyon Cedex 08, France.

Received 25 January 1996; accepted in final form 12 June 1996.

REFERENCES