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

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Favier, Roland, Esperanza Caceres, Laurent Guillon, 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 (R. Favier, E. Caceres, H. Koubi, B. Sempore, M. Sauvain, and H. Spielvogel. J. Appl. Physiol. 80: 650–655, 1996). 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

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 Biologia 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 every 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\textsuperscript{1}) or 15 g of coca leaves (Coca\textsuperscript{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\textsuperscript{1} and Coca\textsuperscript{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\% \(\dot{V}O_{2}\text{peak}\). Identical weights were placed on the pan balance of the bicycle in each trial, and revolutions per minute were closely monitored to ensure identical power outputs in both trials.

At R2 and at 5, 15, 30, 45, and 60 min of the submaximal exercise, heart rate (HR), arterial oxygen saturation (\(S_{a}O_{2}\)), and mean arterial blood pressure (MABP) were recorded and expired air was collected in Douglas bags.

Blood samples were collected before exercise (R1 and R2) and during the 5th, 15th, 30th, and 60th min of cycling. Two milliliters of blood were collected in EDTA for catecholamine, glucose, and FFA determinations. Blood samples (2 ml) for analysis of glucagon and insulin were collected in EDTA with a protease inhibitor, aprotinin (Sigma Chemical).

Analytic methods. HR was measured continuously by bipolar electrocardiographic telemetry (Sport Tester). \(S_{a}O_{2}\) was monitored with an ear oximeter (Ohmeda, Biox 3000). The ear lobe was cleansed and massaged vigorously with an ointment (Trafuril, Ciba-Geigy) to increase perfusion before ear-clip attachment. By use of a cuff around the arm, systolic and diastolic blood pressures were measured with a manual sphygmomanometer. The expired gases were analyzed for volume (Tissot spirometer) and for \(O_{2}\) and \(CO_{2}\) (Servomex 570A, and Gould Capnograph, Mark III, respectively). Subsequently, \(O_{2}\) uptake (\(\dot{V}O_{2}\)), \(CO_{2}\) production, and the RER were calculated. Plasma glucose concentration was determined with a Boehringer kit (Meylan, France). FFAs were determined by the acyl-CoA synthase-acyl oxidase method with a kit (nonesterified fatty acids test; Bioloy). Glycerol concentration was evaluated by an enzymatic method (Boehringer). Lactate was fluorimetrically assayed (16).

Epi and norepinephrine (NE) were assayed by high-performance liquid chromatography with electrochemical detection as described previously (16). Plasma insulin and glucagon were determined by radioimmunoassay with standard kits (CIS Bio International, Gif/Yvette, France, and Pharmacia France, Saint Quentin Yvelines, France, respectively).

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\textsuperscript{1} and Coca\textsuperscript{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\textsuperscript{1}), whereas it decreased significantly subsequent 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\textsuperscript{1} and Coca\textsuperscript{2} trials (Table 4).

Table 1. Summary of characteristics of subjects

| Age, yr | 27.1 ± 1.6 |
| Body weight, kg | 65.6 ± 1.7 |
| Body height, cm | 169.6 ± 1.7 |
| Wmax, W | 185 ± 8 |
| HR\textsubscript{max}, beats/min | 184 ± 3 |
| \(V\dot{O}_{2}\text{peak}, \text{l} \cdot \text{min}^{-1}\) | 2.57 ± 0.07 |
| \(\dot{V}O_{2}\text{peak}, \text{m} \cdot \text{O}_{2} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) | 39.4 ± 0.9 |

Values are means ± SE; nos. in parentheses, range. Wmax, maximal power output; HR\textsubscript{max}, maximal heart rate; \(\dot{V}O_{2}\text{peak}, \text{peak} \text{O}_{2}\) uptake.

Table 2. Plasma hormones and metabolites at rest

<table>
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<tr>
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<th>Coca\textsuperscript{1}</th>
<th>Coca\textsuperscript{2}</th>
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<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>
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<tr>
<td>Insulin, (\mu\text{U}/\text{ml})</td>
<td>15.7 ± 2.3</td>
<td>20.3 ± 2.7</td>
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<tr>
<td>Glucagon, (\mu\text{g}/\text{ml})</td>
<td>179 ± 19</td>
<td>181 ± 0</td>
</tr>
<tr>
<td>Glucose, (\text{mg} / \text{dl} )</td>
<td>5.03 ± 0.25</td>
<td>5.57 ± 0.33</td>
</tr>
<tr>
<td>FFA, (\text{mM})</td>
<td>0.193 ± 0.038</td>
<td>0.181 ± 0.028</td>
</tr>
<tr>
<td>Glyceral, (\text{mM})</td>
<td>0.132 ± 0.007</td>
<td>0.132 ± 0.010</td>
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Values are means ± SE. Coca\textsuperscript{1}, group chewing sugar-free chewing gum; Coca\textsuperscript{2}, 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, epinephrine; NE, norepinephrine; FFA, free fatty acids. †Significantly different from Coca\textsuperscript{1}. ‡Significantly different from R1.

Table 3. Cardiorespiratory variables measured at R2

<table>
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<th>Coca\textsuperscript{1}</th>
<th>Coca\textsuperscript{2}</th>
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<tr>
<td>(V\dot{O}_{2}), \text{l} · \text{min}^{-1})</td>
<td>4.9 ± 0.4</td>
<td>5.2 ± 0.3</td>
</tr>
<tr>
<td>(V\dot{CO}_{2}), \text{l} · \text{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>(V_{E}, \text{l} / \text{min})</td>
<td>12.8 ± 1.0</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>(S_{a}O_{2}), %</td>
<td>94.1 ± 0.6</td>
<td>94.5 ± 0.4</td>
</tr>
<tr>
<td>MABP, mmHg</td>
<td>89 ± 2</td>
<td>93 ± 2</td>
</tr>
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</table>

Values are means ± SE. \(V\dot{O}_{2}\), \text{O}_{2}\) uptake; \(V\dot{CO}_{2}\), \text{CO}_{2}\) production; RER, respiratory exchange ratio; \(V_{E}\), ventilatory output; HR, heart rate; \(S_{a}O_{2}\), arterial \text{O}_{2}\) saturation; MABP, mean arterial blood pressure.
During prolonged exercise, there was a significant effect of coca chewing on $\dot{V}O_2$, CO$_2$ production, RER, and HR, which were all significantly increased in the Coca$^+$ trial (Figs. 1 and 2). Neither SaO$_2$ 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$^-$ 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$^-$ and Coca$^+$ 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

Fig. 3. Hormone exercise-induced changes \(\Delta = \text{values at X (time)} - \text{values at rest after chewing}\) 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.

Fig. 4. Metabolite exercise-induced changes \(\Delta = \text{values at X (time)} - \text{values at rest after chewing}\) 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 Mamani (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 \( \sim 1 \) 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 \( \beta \)-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 altitude exposure for which there was reported an unchanged plasma NE level 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
administration increases gene expression of the rate-limiting enzyme tyrosine hydroxylase in catecholamine biosynthesis. 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 1 trial (11.8 ± 1.1 and 18.8 ± 2.4 μU/ml during the 5th min of exercise for the Coca 1 and Coca 2 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 1 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 1 and Coca 2 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 1 compared with the Coca 2 trial, suggesting a decrease in ɳ. These data contrast with the unchanged ɳ 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 ɳ 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 1 and Coca 2 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.

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