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Article *in* Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology · March 1996

DOI: 10.1152/jappl.1996.80.2.650 · Source: PubMed

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Effects of coca chewing on hormonal and metabolic responses during prolonged submaximal exercise

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Favier, Roland, Esperanza Caceres, Harry Koubi, Brigitte Sempore, Michel Sauvain, and Hilde Spielvogel. Effects of coca chewing on hormonal and metabolic responses during prolonged submaximal exercise. *J. Appl. Physiol.* 80(2): 650–655, 1996.—The effects of coca chewing on prolonged submaximal exercise responses were investigated in chronic coca chewers and compared with a group of nonchewers. At rest, coca chewing during a 1-h period was followed by a significant increase in blood glucose, free fatty acid, and norepinephrine concentrations and a significant reduction in insulin plasma level. During prolonged (1-h) submaximal (65–70% peak O_2 uptake) exercise, chewers displayed a significantly greater adrenergic activation (as evidenced by a higher level of plasma epinephrine) and an increased use of fat (as evidenced by a lower respiratory exchange ratio). The gradual increase in oxygen uptake (O_2 drift) commonly observed during prolonged exercise was blunted in coca chewers. This blunting in O_2 drift is not related to coca-induced changes in ventilatory or lactate responses to exercise but could possibly be related to an enhanced glucose utilization by chewers during the late phase of exercise. The present results provide experimental evidence of the physiological effects of coca chewing that could explain the better ability of coca users to sustain strenuous work for an extended period of time.

epinephrine; norepinephrine; fat metabolism; carbohydrate metabolism; oxygen drift; insulin; glucagon

THE SHRUB *Erythroxylum coca* is widely cultivated in the warm valleys along the eastern slope of the Bolivian and Peruvian Andes. The leaves are known to contain several alkaloids of potential pharmacological importance, of which the best known is cocaine. Andean Indians chew coca leaves in conjunction with the alcaline ashes (lejia) of various edible plants, which facilitates the extraction of these alkaloids. Consumption of coca leaves in Bolivia and Peru has been continuous and extensive. Evidence exists of its use throughout the Andes exists well before the Incan empire (7). According to the users, coca alleviates hunger, cold, and fatigue.

Although Kershner et al. (18) have reported that cocaine administration improved maximal oxygen uptake ($\dot{V}O_{2max}$), we have reported in a companion paper (26) that neither maximal aerobic capacity nor work efficiency is improved by coca chewing. However, in the same study, we found that, during incremental exercise, coca chewing was accompanied by an enhanced fat availability [as evidenced by a higher plasma free fatty acid (FFA) concentration], a condition that is known to improve endurance performance (8, 10). These latter results are contrary to those of previous studies (1, 3, 4, 9) that examined the effects of cocaine administration on exercise performance. Indeed, these authors (1, 3, 4, 9) have shown that cocaine injection before exercise caused a significant reduction in endurance time to exhaustion. This reduced exercising capacity after cocaine injection has been attributed to an elevation of plasma catecholamines (9), which are known to enhance glycogen breakdown (25). It has been documented in both animal and human studies that fatigue, in activities requiring ~60–85% maximal oxygen uptake ($\dot{V}O_2$), is closely associated with muscle glycogen depletion (for a review see Ref. 8). It is thus not surprising to see that cocaine administration resulted in an impaired exercise performance (1, 3, 4, 9). However, these studies were performed in rodents (rats) injected acutely with cocaine hydrochloride and with a dosage approximately three to five times higher than the amount of cocaine that could be extracted by coca chewing. On the one hand, assuming that traditional consumers chew ~10–20 g of coca leaves (which contain ~0.5% of cocaine) daily (7, 26), a dose of ~1–2 mg cocaine$\cdot$kg$^{-1}\cdot$day^{-1} can be calculated, a dose that has been shown not to affect endurance performance, muscle glycogen breakdown, and plasma concentrations of epinephrine (Epi) and norepinephrine (NE) (4). On the other hand, we are not aware of any study that examined the influence of coca chewing on metabolic and hormonal adaptations during prolonged exercise.

Therefore, we designed this study to provide information on the influence of coca chewing on prolonged submaximal exercise performance. For this purpose, we recruited subjects from two rural communities of the Altiplano (Bolivia; mean altitude ~3,800 m) in which we were able to find traditional coca chewers (C) as well as nonchewers (NC). As mentioned in a companion paper (26), each group was only examined according to its customary conditions, i.e., C after coca chewing and NC without chewing. Even though such an experimental design does not address the issue of comparing acute vs. chronic effects of coca chewing, this approach allowed us to evaluate the physiological basis for the improved tolerance to prolonged submaximal exercise claimed by coca users.

METHODS

Subjects. The subjects in this study were 22 men between the ages of 17 and 45 yr. All were natives from the Altiplano and reported that their primary occupation was agriculture.

Genetically, the subjects were Mestizos with a predominantly Aymara admixture. The subjects were instructed about the protocol before they gave their informed consent for participation. Before initiation of the experiment, each volunteer was examined by a physician and was deemed free of any cardiovascular or pulmonary disease. The subjects were divided into two groups: the first (n = 14) consisted of NC (i.e., subjects chewing <3 times/yr), whereas the second (C; n = 8) was composed of traditional coca users (i.e., subjects chewing >3–4 times/wk during work in the field). 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). All measurements were performed at the Instituto Boliviano de Biologia de Altura (La Paz, Bolivia; mean altitude = 3,600 m).

To minimize factors of learning that could affect exercise performance, each subject performed an incremental test on a bicycle ergometer with a mechanical braking system. On the next day, the subject rested in a chair for 1 h. During this period, the coca users were invited to chew their customary quantity of coca leaves. Thereafter, peak oxygen uptake ($\dot{V}O_{2peak}$) was measured in the same way as on the day of familiarization by using a continuous progressive protocol as described in detail elsewhere (26). Briefly, the subjects completed an incremental exhaustive cycling exercise protocol in which the workload was increased by 30 W/min. The subjects cycled at 70 rpm on a cycle ergometer (Ergomeca) and were paced with a metronome. Initially, the subjects pedaled for 4 min at 60 W and continued pedaling as the workload was increased by 30-W increments every 4 min until exhaustion. $\dot{V}O_{2peak}$ measured in these conditions was used to determine the workload to be used for the submaximal exercise test.

Submaximal exercise test. One week after $\dot{V}O_{2peak}$ determination, the subjects performed a steady-state exercise. A submaximal workload was chosen individually to obtain a $\dot{V}O_2$ that was 65–70% of $\dot{V}O_{2peak}$. Before the test, the subjects abstained from vigorous exercise and the C were asked to abstain from coca chewing until the next day. When all the subjects reported to the laboratory after an overnight fast, they were provided, 3 h before the exercise trial, with a light standardized breakfast (mainly bread without fats). They were allowed to drink cañawa juice. Cañawa is an Andean grain like quinua. They were prohibited from having tea or coffee.

Heart rate was monitored continuously by bipolar electrocardiographic telemetry (Sport Tester). Arterial oxygen saturation was monitored continuously with an ear oximeter (Biox 3000, Ohmeda). The ear lobe was cleansed and massaged vigorously to increase perfusion before ear-clip attachment.

A small catheter was inserted into an antecubital vein, and the subject rested in a chair for 1 h. During this period, the coca users were invited to chew their customary quantity of coca leaves.

Respiratory gas exchanges and blood samples were obtained twice at rest and before and after coca chewing in coca users. The same timing protocol was used for NC, and, in this case, the two resting samples were separated by 1 h during which the subjects only rested quietly in a chair. The subjects were then seated on the cycle ergometer where they exercised for 60 min at a work rate chosen to elicit 65–70% of $\dot{V}O_{2peak}$. Blood was withdrawn during exercise at 15, 30, and 60 min. From each blood sample, a 0.5-ml aliquot was deproteinized by adding 1.0 ml of ice-cold 10% $HClO_4$. The acid extract was separated by centrifugation and neutralized with KOH. 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, apoprotinin (Sigma Chemical). The total blood volume removal averaged 22.5 ml (5 × 4.5 ml).

Analytical methods. Plasma glucose concentration was determined with a Boerhinger kit (Meylan). FFAs were determined by the acyl CoA synthase-acyl oxidase method with a kit (nonesterified fatty acids test, Biolyon). Glycerol concentration was evaluated by an enzymatic method (Boerhinger, Meylan). Lactate was fluorimetrically assayed (20).

Epi and NE were assayed by high-performance liquid chromatography with electrochemical detection, as described previously (19). Plasma insulin and glucagon were determined by radioimmunoassay with standard kits.

Statistical analysis. Data are presented as means ± SE. Comparisons were made using a two-way (coca-by-time) analysis of variance followed by a post hoc test (Fisher's protected least squares difference). The level of significance was set at 5%.

RESULTS

The amount of coca leaves used by the C averaged 16 g in addition to 1.3 g of alkaline ashes (lejia) used to increase the extraction of the alkaloids.

The anthropometric data of the NC and C are reported in Table 1. The anthropological characteristics and $\dot{V}O_{2peak}$ were similar in the two groups.

At rest, before chewing, the C displayed a significantly lower plasma insulin level and a higher Epi concentration compared with the NC (Table 2). The influence of 1 h of mastication of coca leaves on resting plasma metabolites and hormones controlling glucose homeostasis is reported in Table 2. Subsequent to coca chewing, the C were characterized by a significant increase in plasma glucose, FFA, and NE. C again had a significantly lower circulating insulin level after chewing (Table 2).

The respiratory gas exchanges, circulatory variables, plasma metabolites, and glucoregulatory hormones during the 1-h submaximal exercise bout are reported in Tables 3 and 4. The mean power output during 1 h of exercise averaged 110 ± 5 W in NC and 104 ± 5 W in C, which represents 62.0 ± 2.1 and 62.0 ± 6.1% of the maximal power output for NC and C, respectively.

There was a significant interaction between exercise duration and coca chewing on absolute $\dot{V}O_2$ (in l/min) and relative $\dot{V}O_2$ (in $ml \cdot min^{-1} \cdot kg^{-1}$) during prolonged

Table 1. *Anthropometric characteristics and $\dot{V}O_{2peak}$ of subjects*

	NC	C
Age, yr	30.7 ± 1.7	32.9 ± 2.1
Body weight, kg	60.8 ± 1.8	58.9 ± 1.8
Body height, m	1.62 ± 0.01	1.61 ± 0.01
Body mass index, kg/m^2	23.1 ± 0.6	22.8 ± 0.6
Body surface area, m^2	1.64 ± 0.02	1.61 ± 0.03
Amount of coca leaves, g		15.7 ± 2.0
Amount of lejia, g		1.3 ± 0.4
Coca use duration, yr		8.6 ± 2.7
$\dot{V}O_{2peak}$, $ml \cdot min^{-1} \cdot kg^{-1}$	42.4 ± 1.6	42.8 ± 1.8

Values are means ± SE. $\dot{V}O_{2peak}$, peak O_2 uptake; NC, nonchewers; C, chewers.

Table 2. *Plasma metabolite and hormonal concentrations measured at rest before and after coca chewing*

	NC		C		Main Effects		
	R1	R2	R1	R2	Time	Coca	Time-coca interaction
Glucose, mM	4.9 ± 0.3	4.9 ± 0.3	4.2 ± 0.2	4.9 ± 0.1*	$P<0.05$	NS	NS
FFA, μM	218 ± 40	205 ± 28	218 ± 65	332 ± 81*	$P<0.01$	NS	$P<0.01$
Glycerol, μM	158 ± 11	166 ± 11	161 ± 23	153 ± 12	NS	NS	NS
Lactate, mM	1.5 ± 0.1	1.5 ± 0.1	1.2 ± 0.1	2.0 ± 0.6	NS	NS	NS
Epi, pg/ml	41 ± 1	52 ± 4*	64 ± 16†	69 ± 13	NS	$P=0.06$	NS
NE, pg/ml	524 ± 76	656 ± 50	580 ± 93	785 ± 177*	$P<0.01$	NS	$P<0.01$
Insulin, μU/ml	16.8 ± 1.5	18.2 ± 1.6	12.2 ± 1.4†	14.0 ± 1.9†	NS	$P<0.05$	NS
Glucagon, pg/ml	130 ± 12	143 ± 16	148 ± 16	147 ± 28	NS	NS	NS

Values are means ± SE. R1, before chewing; R2, after chewing; FFA, free fatty acids; Epi, epinephrine; NE, norepinephrine; NS, not significant. For NC, R1 and R2 are separated by 1 h during which subjects rested quietly in a chair. See METHODS for more details. Significantly different from: *R1; †NC.

exercise (Table 3). Thus, $\dot{V}O_2$ increased progressively in NC from 15 to 60 min of exercise, whereas it was stable in C throughout the exercise bout.

The respiratory exchange ratio (RER) was significantly lower in C from 30 to 60 min of exercise (Table 3).

Although plasma FFAs tended to be higher in C compared with NC throughout the exercise, there was no significant effect of coca chewing on circulating FFAs (Table 4).

Plasma Epi was significantly increased by chewing in C (Table 4, Fig. 1). On the other hand, the exercise-induced drop of insulin was significantly reduced, whereas plasma glucagon was significantly higher in C (Fig. 1).

DISCUSSION

Nutritional status is one of many factors that can modify prolonged exercise performance. Indeed, it was claimed that coca use results in a loss of appetite and reduced consumption of food (15). It was thus important to verify that our subjects were appropriately nourished and that the differences observed between NC and C were not related to factors other than coca mastication. A dietary survey of the two communities showed that the energy intake was similar in NC and C (C. Lujan and J. L. San Miguel, unpublished data). It needs, however, to be underlined that the diet of these agriculturalists was rich in carbohydrates (84% of the calories) and low in fat (~6%), in agreement with previous reported data (23). Whether this dietetic pattern is a consequence of socioeconomic conditions or an adaptive selection to life at high altitude is not known. The body mass index [weight (kg)/height (m^2)] has been shown to be a relatively good measure of nutritional status (12). From the data reported in Table 1, it can be concluded that both groups of subjects were not nutritionally deficient, and there was no influence of coca use on nutritional status. It has to be mentioned that plasma insulin was lower in C before chewing (Table 2). It is unlikely that it was linked to acute

Table 3. *Metabolic changes during prolonged (1-h) submaximal exercise in NC and C*

	Exercise Duration, min				Main Effects		
	15	30	45	60	ExDur	Coca	ExDur-coca interaction
			NC				
$\dot{V}O_2$, l/min	1.93 ± 0.06	1.95 ± 0.06	2.01 ± 0.08	2.15 ± 0.09	$P<0.01$		
$\dot{V}O_2$, ml·min^{-1}·kg^{-1}	31.8 ± 1.0	32.2 ± 1.0	33.1 ± 1.3	35.4 ± 1.5	$P<0.01$		
$\dot{V}E$, l/min	67.1 ± 2.2	69.2 ± 2.6	72.9 ± 4.1	78.0 ± 4.6	$P<0.01$		
$\dot{V}E/\dot{V}O_2$, l BTPS/l STPD	35.7 ± 1.0	36.3 ± 1.1	36.9 ± 1.1	36.1 ± 1.9	NS		
HR, beats/min	137 ± 4	143 ± 4	148 ± 4	153 ± 4	NS		
MABP, Torr	91.6 ± 1.7	91.6 ± 1.8	92.3 ± 1.8	91.1 ± 1.7	NS		
Sa_{O_2}, %	92.2 ± 0.8	91.6 ± 0.7	91.7 ± 0.6	91.7 ± 0.5	NS		
RER	0.98 ± 0.01	0.97 ± 0.02	0.95 ± 0.02	0.94 ± 0.02	$P<0.01$		
			C				
$\dot{V}O_2$, l/min	1.87 ± 0.10	1.92 ± 0.11	1.97 ± 0.10	1.93 ± 0.10	$P<0.001$	NS	$P<0.05$
$\dot{V}O_2$, ml·min^{-1}·kg^{-1}	32.0 ± 1.5	32.6 ± 1.7	33.6 ± 1.5	32.9 ± 1.5	$P<0.001$	NS	$P<0.05$
$\dot{V}E$, l/min	68.4 ± 4.1	70.8 ± 5.3	72.9 ± 4.1	70.9 ± 3.3	$P<0.001$	NS	NS
$\dot{V}E/\dot{V}O_2$, l BTPS/l STPD	38.3 ± 2.1	38.6 ± 2.1	39.9 ± 2.4	39.9 ± 2.3	NS	NS	NS
HR, beats/min	144 ± 5	153 ± 4	156 ± 3	159 ± 3	$P<0.001$	NS	NS
MABP, Torr	96.8 ± 2.4	94.2 ± 2.7	93.9 ± 2.6	93.3 ± 1.9	NS	NS	NS
Sa_{O_2}, %	90.9 ± 0.9	89.8 ± 1.0	91.1 ± 0.7	90.8 ± 0.6	NS	NS	NS
RER	0.93 ± 0.03	0.89 ± 0.02*	0.89 ± 0.03*	0.87 ± 0.03*	$P<0.001$	$P<0.05$	NS

Values are means ± SE. ExDur, exercise duration; $\dot{V}O_2$, oxygen uptake; $\dot{V}E$, ventilatory output; $\dot{V}E/\dot{V}O_2$, ventilatory equivalent; HR, heart rate; MABP, mean arterial blood pressure; Sa_{O_2}, arterial O_2 saturation; RER, respiratory exchange ratio. *Significantly different from NC.

Table 4. *Hormonal and plasma metabolite changes during prolonged (1-h) submaximal exercise in NC and C*

	Exercise Duration, min			Main Effects		
	15	30	60	ExDur	Coca	ExDur-coca interaction
			NC			
Glucose, mM	4.8 ± 0.2	5.0 ± 0.2	5.3 ± 0.2	$P < 0.01$		
FFA, μM	184 ± 32	198 ± 36	384 ± 84	$P < 0.001$		
Glycerol, μM	144 ± 17	169 ± 16	192 ± 15	$P < 0.001$		
Lactate, mM	4.0 ± 0.5	3.6 ± 0.5	3.1 ± 0.4	$P < 0.001$		
Epi, pg/ml	104 ± 14	144 ± 18	193 ± 27	$P < 0.001$		
NE, pg/ml	908 ± 72	1,109 ± 93	1,385 ± 170	$P < 0.001$		
Insulin, μU/ml	11.0 ± 1.4	10.1 ± 1.3	8.7 ± 0.7	$P < 0.001$		
Glucagon, pg/ml	137 ± 11	132 ± 11	135 ± 13	NS		
			C			
Glucose, mM	4.9 ± 0.1	4.8 ± 0.1	4.6 ± 0.1	NS	NS	$P < 0.02$
FFA, μM	204 ± 61	258 ± 42	509 ± 46	$P < 0.001$	NS	NS
Glycerol, μM	157 ± 23	175 ± 24	220 ± 23	$P < 0.001$	NS	NS
Lactate, mM	4.3 ± 0.9	4.0 ± 1.0	3.4 ± 0.8	$P < 0.001$	NS	NS
Epi, pg/ml	197 ± 52	239 ± 70	306 ± 75	$P < 0.001$	$P < 0.05$	NS
NE, pg/ml	1,243 ± 186	1,253 ± 222	1,476 ± 298	$P < 0.001$	NS	NS
Insulin, μU/ml	9.3 ± 0.9	8.9 ± 0.9	6.8 ± 1.2	$P < 0.001$	$P < 0.05$	NS
Glucagon, pg/ml	149 ± 32	175 ± 45	168 ± 33	NS	NS	NS

Values are means ± SE.

nutritional factors because both groups of subjects were provided with a standardized breakfast 3 h before the test after an overnight fast. In addition, C were asked to abstain from coca chewing for 24 h before the exercise bout. The lower plasma insulin of C was either due to some residual effects of chronic coca use (e.g., increased sensitivity of β-pancreatic cells) or to a substantial plasma cocaine level in C even before chewing. Unfortunately, we did not measure cocaine concentration in blood before chewing, but this latter possibility seems questionable. Indeed, it was reported (21) that plasma cocaine was undectectable in chronic coca users before chewing, peaked at ~90–100 ng/ml after subjects chewed 12 g of coca leaves, remained at this level for 1 h after chewing was stopped, and then disappeared with an elimination half-life of 4–6 h.

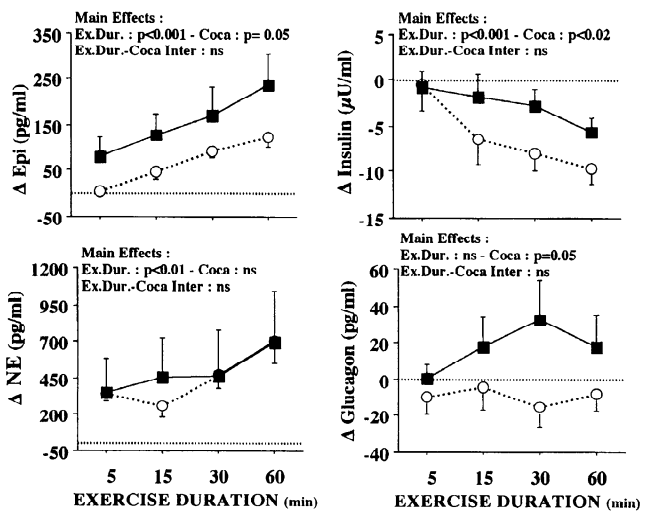

Fig. 1. Hormonal exercise-induced changes during prolonged exercise in nonchewers (○) and chewers (■). Epi, epinephrine; NE, norepinephrine; Ex.Dur., exercise duration; Inter, interaction; ns, not significant. Δ, Value at *time x* − value after chewing; horizontal dotted line, baseline. Values are means ± SE.

Effects of coca chewing on metabolic and hormonal status at rest. Acute coca chewing did not have any impact on basal heart rate, arterial oxygen saturation, or mean arterial blood pressure (data not shown). However, it was accompanied by some metabolic and hormonal modifications. Thus a significant increase in plasma glucose, FFA, and NE levels were observed in the C (Table 2). Cocaine sympathomimetic actions have been described as early as 1910 (see review in Ref. 13), and recently Conlee et al. (9) have reported that acute cocaine administration resulted in an increase not only of NE but also of Epi and dopamine. In the case of coca chewing, we found that, at rest, only NE was elevated; this increased plasma NE level was probably due to the blockade of NE reuptake at the sympathetic nerve endings (13). It is likely that the adrenal (Epi) stimulation observed by Conlee et al. (9) was related to the large amount of cocaine administered (12.5 mg/kg). Indeed, on the assumption that coca leaves contain 0.4–0.7% of cocaine (M. Sauvain, unpublished data), such a dose would be equivalent to chewing 100–190 g of coca leaves, i.e., a quantity 6–12 times greater than the mean quantity of coca leaves chewed by our subjects (Table 1). Many investigators believe that NE reuptake blockade alone could not account for the extent of cocaine sympathomimetic actions because cocaine also may potentiate catecholamine-receptor sensitivity (13, 29). The lower insulin level measured at rest in C is no doubt a contributing factor in the pronounced fat mobilization and the significant increase in blood glucose observed in coca C (Table 2). The acute effects of coca chewing on plasma FFA level have been discussed in detail in a companion paper (26). In that study, we hypothesized that at least part of the increase in plasma FFAs after coca chewing was related

to changes in the rate of reesterification of FFA due to NE-induced vasoconstriction, causing decreased splanchnic blood flow.

Effects of coca chewing on subsequent metabolic and hormonal responses to submaximal exercise. The impact of coca mastication on metabolic and hormonal responses to submaximal exercise is reported in Tables 3 and 4. Thus it appeared that during prolonged submaximal exercise, C displayed a significantly greater circulating Epi (Table 4, Fig. 1) in conjunction with a lower RER (Table 3). One must recognize the limitations of using the RER to reflect metabolism. It is certainly possible that hyperventilation and disturbances in acid-base balance can create artifacts in the RER. However, in the present study in which exercise was prolonged, blood lactate concentration decreased from 15 to 60 min of exercise (Table 4), suggesting that changes in acid-base status were not responsible for the reduced RER observed in C. On the other hand, changes in ventilatory output and ventilatory equivalent from 30 to 60 min of exercise were similar in NC and C (Table 3). It has been demonstrated that the increased availability of plasma FFAs resulted in a diminished dependence on muscle glycogen during exercise (10), and such a sparing of muscle glycogen has been shown to delay the onset of exhaustion (8). In addition, we found that the rate of lipolysis (as assessed by changes in plasma glycerol) was similar in C and NC during the first 15 min of exercise, but, at the same time, plasma FFAs dropped significantly more in C (129 ± 44 μM) than in NC (29 ± 15 μM). Thus the data, although limited, do suggest that fat metabolism was enhanced by coca chewing under the present exercise conditions.

In the present study, we cannot attempt to determine whether fat metabolism downregulates carbohydrate use. However, the exercise-induced hormonal changes observed in C (Fig. 1) would suggest that they should increase hepatic glycogenolysis and gluconeogenesis during exercise (28). Indeed, in the presence of a decrement in insulin such as observed in C (Table 4), the liver becomes so sensitive to the effects of glucagon that an increase in glucose production will result from a minimal increase in the level of this hormone (28). Nevertheless, plasma glucose decreased in C from 15 to 60 min of exercise ($P < 0.02$), suggesting that glucose utilization exceeded glucose production by the liver. In addition, Bracken and co-workers (3, 4) and Conlee et al. (9) reported that cocaine administration at high doses (12.5–20 mg/kg) accelerates muscle glycogen breakdown (4, 9) and reduces exercise endurance (3). By contrast, with low doses of cocaine (0.1–2.5 mg/kg), neither running time to exhaustion nor rate of glycogen breakdown was affected (4). Muscle glycogenolysis during exercise is controlled by muscle contraction during which calcium released from the sarcoplasmic reticulum increases phosphorylase *a* activity and by Epi, which, by increasing adenosine 3′,5′-cyclic monophosphate generation, sets in motion the cascade reaction leading to the conversion phosphorylase *b* to phosphorylase *a* (25). Recently, it was demonstrated that the cocaine-induced dopamine release in the nucleus accumbens via a calcium-dependent mechanism can be prevented by the use of the dihydropyridine calcium-channel antagonist (22). It can be thus hypothesized that cocaine at a low dose could affect muscle glycogenolysis through Epi and Ca-dependent mechanisms. To clarify these issues, it would be necessary to use the isolated perfused rat hindquarter preparation.

The metabolic and hormonal responses during submaximal exercise after coca chewing are reminiscent of those observed after caffeine ingestion (2, 27). Indeed, these authors reported that caffeine administration is characterized by a lower RER, a sympathoadrenergic activation, and increased circulating FFAs. Whether caffeine and coca use share the same molecular mechanism(s) to improve fat mobilization and utilization remains to be determined, but both of these drugs can potentially improve performance (2, 27).

$\dot{V}O_2$ has been shown to gradually increase during prolonged submaximal constant-rate exercise, a phenomenon that has been referred to as $\dot{V}O_2$ drift (see, e.g., Ref. 17). Several putative mechanisms for this observation have been proposed, such as reduction in mechanical efficiency, increased ventilation, alteration in substrate use, increased circulatory catecholamines, lactate accumulation, and exercise-induced hyperthermia. Recently, it was shown that the $\dot{V}O_2$ drift reflects predominantly increased $\dot{V}O_2$ by the exercising legs (24). In the present study, we found that the slow increase in $\dot{V}O_2$ from 15 to 60 min of exercise observed in NC was blunted by coca chewing (Table 3). It did not seem that this blunting was related to coca-induced changes in plasma catecholamines because Epi accumulation during exercise was similar in NC and C (Fig. 1). These data are in agreement with a recent study by Gaesser et al. (14), who showed that Epi does not contribute significantly to the $\dot{V}O_2$ drift during exercise. Even though some authors (6) assumed that the net lactate accumulation in the exercising muscles was indeed the cause of $\dot{V}O_2$ drift and, although we did not measure muscle lactate, blood lactate kinetics during the submaximal test was similar in C and NC (Table 4). As a consequence, it can be concluded that, in our experimental conditions, changes in lactate metabolism would not seem to be a determinant cause of the $\dot{V}O_2$ drift, in agreement with recent data (14). Recently, Hamilton et al. (16) have reported that the $\dot{V}O_2$ drift can be totally prevented by glucose infusion, suggesting that glucose utilization could be one of the contributors to the gradual increase of $\dot{V}O_2$ during prolonged exercise. In the present study, we found that in NC plasma glucose increased gradually from 15 to 60 min of exercise, whereas at the same time it decreased in C (Table 4), and that there was a significant interaction between exercise duration and coca chewing ($P < 0.02$). It is therefore possible that the increase in glucose utilization in C when exercise is prolonged could be somewhat related to the blunting of the $\dot{V}O_2$ drift. At first glance, it seems that the increased glucose use by C is in apparent conflict with an enhanced lipid metabolism (cf. above). Such an apparent contradiction can

also be observed during altitude acclimatization, which was reported to enhance fat metabolism (30) simultaneously to an increased utilization of blood glucose during exercise (5).

In conclusion, our results demonstrate that coca chewing before exercise enhanced FFA availability and increased plasma glucose. During 1 h of submaximal exercise, coca chewing modified the hormonal and metabolic responses in such a way that indicates that fat mobilization and utilization are enhanced. Such a shift in substrate use could possibly spare glycogen stores and delay exhaustion. In addition, the O_2 drift that occurs naturally during prolonged exercise is blunted by coca chewing, suggesting that coca C could exercise for a longer period before $\dot{V}O_2$ reaches its maximum. It is not known, however, whether the metabolic and hormonal changes induced by coca chewing are sufficient to postpone fatigue if exercise is prolonged for several hours.

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 supported by a grant from Ministère des Affaires Etrangères (France).

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Received 6 March 1995; accepted in final form 15 September 1995.

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