Cocaine and exercise: α-1 receptor blockade does not alter muscle glycogenolysis or blood lactacidosis

ROBERT K. CONLEE, K. PATRICK KELLY, EDWARD O. OJUKA, AND ROGER L. HAMMER
Human Performance Research Center, Brigham Young University, Provo, Utah 84602

Conlee, Robert K., K. Patrick Kelly, Edward O. Ojuka, and Roger L. Hammer. Cocaine and exercise: α-1 receptor blockade does not alter muscle glycogenolysis or blood lactacidosis. J. Appl. Physiol. 88: 77-81, 2000.—In our previous work, we routinely observed that a combined cocaine-exercise challenge results in an abnormally rapid muscle glycogen depletion and excessive blood lactacidosis. These phenomena occur simultaneously with a rapid rise in norepinephrine and in the absence of any rise in epinephrine. We postulated that norepinephrine may cause vasocostriction of the muscle vasculature through activation of α-1 receptors during cocaine-exercise, thus inducing hypoxia and a concomitant rise in glycogenolysis and lactate accumulation. To test this hypothesis, rats were pretreated with the selective α-1-receptor antagonist prazosin (P) (0.1 mg/kg iv) or saline (S). Ten minutes later, the animals were treated with cocaine (-C) (5 mg/kg iv) or saline (-S) and run for 4 or 15 min at 22 m/min at 10% grade. In the S-S group, glycogen content of the white vastus lateralis muscle was unaffected by exercise at both time intervals, whereas in S-C rats glycogen was reduced by 47%. This effect of cocaine-exercise challenge was not attenuated by P. Similarly, blood lactate concentration in S-C rats was threefold higher than that of S-S after exercise, a response also not altered by pretreatment with P. On the basis of these observations, we conclude that the excessive glycogenolysis and lactacidosis observed during cocaine-exercise challenge is not the result of vasocostriction secondary to norepinephrine activation of α-1 receptors.

METHODS

Animal preparation. Male Sprague-Dawley rats were obtained from Sasco Labs (Omaha, NE) and housed in animal quarters in which the temperature (23–25°C) and lighting (12:12-h light-dark cycle, lights 0700–1900) were automatically controlled. Food and water were provided ad libitum. The animals were conditioned to run on a motor-driven treadmill over a 2- to 3-wk period until they were running continuously for 30 min at 22 m/min and 10% grade. This exercise intensity is considered moderate to heavy.

Three to four days before the experiment, catheters were implanted into the right jugular vein under ketamine/acepromazine maleate anesthesia as described previously (12). The catheter was used for drug or saline administration, for blood sampling during the test, and for administration of the anesthesia at the end of the experiment.

Experimental design and testing procedures. Ten minutes before rest or exercise began and while the animals were sitting still on the treadmill, they were pretreated with either saline (1 ml/kg iv) or prazosin (0.1 mg/kg iv) (5). This dose of prazosin; carbohydrate metabolism

WE HAVE SHOWN in numerous reports that when exercise is performed after cocaine administration, the combined effect of the two stressors is an abnormally rapid reduction in muscle glycogen and an elevation in blood lactic acid greater than that observed for either treatment alone (2-4, 9, 14, 18). These observations have become our markers in studies involving various combinations of cocaine and exercise and are the parameters used to ascertain the mechanism by which cocaine exerts its disruptive effects on the physiology of exercise. We have speculated that these effects of cocaine are mediated by the elevation in catecholamines induced by the drug (6, 8-10, 15). To test that assumption, Ojuka et al. (18) adrenomedullated rats and exposed them to cocaine-exercise challenge. The adrenomedullation eliminated the expected elevation in epinephrine but did not eliminate the elevation in lactate or the reduction in muscle glycogen. The authors concluded that epinephrine was not responsible for the metabolic effects of cocaine during exercise.

Recently Han et al. (12) studied the temporal responses of blood lactate, epinephrine, and norepinephrine during a cocaine-exercise challenge. They observed that the dramatic rise in lactate, which occurred within the first 3 min of the onset of cocaine-exercise, was mirrored by a large rise in norepinephrine. On the other hand, epinephrine concentrations rose more slowly and peaked several minutes later. Norepinephrine levels during cocaine-exercise were 27 times higher than resting levels, 5 times higher than the effects of cocaine alone, and 4 times higher than during exercise alone. The authors postulated that the extreme levels of norepinephrine may have induced vasocostriction of the muscle vasculature through α-1 receptors during the onset of exercise, which would have reduced blood flow and oxygen delivery. The hypoxia would have caused the working muscles to rely on anaerobic sources for energy production, leading to a more rapid glycogen degradation and increased lactate production. The present investigation was designed to test that hypothesis. By using the changes in muscle glycogen and blood lactate as markers, animals were pretreated with prazosin, an α-1 catecholamine receptor antagonist (20), and exposed to a cocaine-exercise test. Data from those animals were compared with data obtained from control animals pretreated with saline and exercised under similar cocaine conditions.
prazosin prevented the rise in blood pressure produced by phenylephrine (5 μg) in a separate group of rats that were prepared for blood pressure recordings with carotid artery catheters. Ten minutes after pretreatment, a blood sample was obtained to determine resting lactic acid. Then, animals that had been randomly assigned to exercise began running on the treadmill as the speed gradually increased from 0 to 22 m/min at 10% grade over a 45-s interval. Simultaneously, saline (1 ml/kg) or cocaine (cocaine·HCl; Sigma Chemical, St. Louis, MO; 5 mg/kg) was administered intravenously. The animals ran for either 4 or 15 min, with blood samples obtained at both times while the animals were running. Animals that had been randomly assigned to rest sat quietly on the treadmill for 15 min after injection of saline or cocaine. The design resulted in the following treatment groups: saline pretreated-saline treated (S-S), prazosin pretreated-saline treated (P-S), saline pretreated-cocaine treated (S-C), and prazosin pretreated-cocaine treated (P-C). Animals from each treatment group experienced the rest or exercise conditions described above.

After the prescribed rest or run, the animals were anesthetized with pentobarbital sodium (60 mg/kg iv). Portions of the soleus, white vastus lateralis, and red vastus lateralis muscles were excised, frozen in aluminum tongs cooled in liquid nitrogen, and stored frozen until assayed for glycogen and lactic acid content.

Biochemical analysis. Plasma lactate was determined from centrifuged blood samples by using an Analox GM 7 Microstat analyzer (InterCon, Champaign, IL). Muscle glycogen content was determined by using the anthrone method of Hassid and Abraham (13). Muscle lactate was extracted from frozen muscle with perchloric acid. The hydrolysate was neutralized with imidazole buffer, and lactate concentrations were measured by using the Analox GM 7 Microstat analyzer.

Statistical analysis. Data were analyzed by using a one-way ANOVA. Group means were compared by using Fisher’s pairwise post hoc test. Significance was declared at the P < 0.05 (one-tail) level of confidence. A one-tail test was appropriate because our hypothesis was that prazosin would block the effects of cocaine during exercise, and, therefore, the prazosin-cocaine values for white vastus muscle glycogen would be higher and the blood lactate values would be lower than those of saline-cocaine.

RESULTS

The glycogen data are presented in Table 1. Neither cocaine nor prazosin had any effect on muscle glycogen content at rest. Exercise alone for 4 or 15 min was effective in decreasing glycogen in red vastus and soleus muscles but not in white vastus muscle in the S-S control group. In contrast, cocaine-exercise (S-C) for 4 or 15 min resulted in a marked depletion of glycogen in white vastus muscle. This effect of cocaine-exercise was not altered by the preadministration of prazosin (P-C). Cocaine-exercise, with (P-C) or without (S-C) prazosin, had no effect on the glycogen content of red vastus or soleus muscles that was different from that of exercise alone (S-S).

The blood lactate data are shown in Table 2. Cocaine-exercise (S-C) for 4 and 15 min resulted in nearly a threefold increase in blood lactate content compared with saline-exercise (S-S). This effect was not attenuated by prazosin pretreatment (P-C). Prazosin pretreatment had no effect on resting lactate levels either (P-S).

<table>
<thead>
<tr>
<th>Condition</th>
<th>S-S (n = 5–7)</th>
<th>P-S (n = 5–8)</th>
<th>S-C (n = 6–9)</th>
<th>P-C (n = 6–10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.2</td>
<td>1.3 ± 0.7</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>(n = 14)</td>
<td>(n = 13)</td>
<td>(n = 15)</td>
<td>(n = 18)</td>
<td></td>
</tr>
<tr>
<td>4-min Ex</td>
<td>3.6 ± 0.8</td>
<td>5.4 ± 1.9</td>
<td>10.8 ± 5.4*</td>
<td>10.1 ± 3.5*</td>
</tr>
<tr>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 13)</td>
<td>(n = 16)</td>
<td></td>
</tr>
<tr>
<td>15-min Ex</td>
<td>3.1 ± 1.4</td>
<td>6.1 ± 1.9</td>
<td>7.7 ± 6.7*</td>
<td>10.2 ± 4.6*</td>
</tr>
<tr>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 13)</td>
<td>(n = 16)</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. * Denotes significantly different from S-S; P < 0.05. All exercise values are significantly different from rest.

Table 1. Effects of cocaine on muscle glycogen concentration (μmol/g) at rest or exercise with or without prazosin pretreatment (α-1 receptor blockade)

The muscle lactate data are shown in Table 3. There was no statistically significant effect of exercise or cocaine in either the red vastus or soleus muscles at either 4 or 15 min, although a trend appeared for a cocaine-exercise-induced increase in the red vastus in the 4-min group. On the other hand, there was a dramatic increase in muscle lactate in the white vastus muscle in all treatment groups at 4 min of exercise that had dissipated by 15 min. The exercise-cocaine data contained considerable variability, as reflected by the SDs. As a result, we could not detect a treatment effect of either cocaine or prazosin beyond that of saline-exercise alone.

DISCUSSION

The purpose of this study was to determine whether α-1 receptor blockade with prazosin would eliminate the predictable effects of cocaine-exercise. The combination of cocaine and exercise has been shown in numerous reports to result in a rapid depletion of white vastus muscle glycogen and a simultaneous increase in blood lactic acid (2–4, 9, 14, 18). We were successful in repeating those findings in the present study and used them as our markers to test our hypothesis. We hypothesized that these metabolic changes in the cocaine

Table 2. Effects of cocaine on blood lactate concentration (mM) at rest or exercise with or without prazosin pretreatment (α-1 receptor blockade)
condition may result from an interruption in blood flow and oxygen delivery to working muscle due to a norepinephrine-induced vasoconstriction of the vasculature serving that tissue. Although we did not measure blood flow directly, we assumed we could interpret our findings to be the result of blood flow alterations for the following reasons. First, Branch and Knuepfer (5) had shown that cocaine causes vasoconstriction through an α-1 receptor-mediated process resulting from the cocaine-stimulated release of norepinephrine from the sympathetic nerve endings (20). Second, it is generally accepted that norepinephrine secretion induced by sympathetic stimulation causes the vasoconstriction responsible for the redistribution of blood flow observed during exercise, and it has been hypothesized that norepinephrine spillover is responsible for the vasoconstriction of working muscle vasculature during intense exercise (19). Third, we had previously observed a very dramatic rise in norepinephrine at the onset of a cocaine-exercise challenge similar to the one employed in the present study (12). And fourth, because prazosin is an α-1 receptor antagonist, we believed that it would block the effects of norepinephrine and, consequently, alter blood flow and eliminate the fall in muscle glycogen and the rise in lactate observed in the cocaine-exercise test. In our pilot study, prazosin was effective in blocking the standard increase in blood pressure induced by an intravenous injection of phenylephrine. Unfortunately, the data of Tables 1 and 2 clearly show that prazosin pretreatment had no effect on the cocaine-exercise-induced depletion of glycogen and the subsequent rise in blood lactate. Therefore, we reject our hypothesis that the enhanced rate of glycogen degradation and increased lactate production were induced by vasoconstriction of the muscle vasculature through α-1 receptor interaction with norepinephrine.

In two previous studies (4, 18), we observed that cocaine-exercise compared with saline-exercise challenges resulted in higher lactate concentrations in red and white vastus muscle that correlated with a greater reduction in muscle glycogen and an exaggerated rise in blood lactate. We concluded that the elevated blood lactate observed in cocaine-exercise resulted from the elevated muscle lactate (4, 18). In the present study, lactates were elevated in white vastus muscle in all treatment groups, including the control, after 4 min of exercise; because of the high variability in the data, we were unable to factor out a specific cocaine-exercise effect (Table 3). On the other hand, there was a tendency for a rise in lactate concentration in the red vastus muscle only in the two cocaine-exercise groups (S-C, P-C, Table 3), as would be anticipated based on previous results (4, 18), but the difference did not reach statistical significance. Therefore, because of the high variability associated with the muscle lactate data, definitive conclusions are risky. Nevertheless, the pattern of the changes in the red vastus muscle coupled with the presence of very high individual lactate values in the white vastus muscle in both S-C and P-C groups at 4 min of exercise supports our conclusion that prazosin was ineffective, and, therefore, the buildup of lactate is not due to the norepinephrine-induced vasoconstrictive effects of the cocaine. The fact that lactate also accumulated in the white vastus in S-S and P-S after 4 min of exercise explains why we observed a rise in blood lactate in these groups (Table 2) and why Han et al. (12) also observed elevated blood lactates after 4 min in their saline-exercise group. What is not clear from these results is why blood lactate is higher in the cocaine-exercise animals if muscle is accumulating lactate in all groups in the first 4 min of exercise. We believe that the variability in the muscle lactate data obscured a real difference between groups and that there really is a greater accumulation in the cocaine-exercise groups that leads to a greater blood level. This conclusion is supported by our previous studies (4, 18).

Another explanation for elevated blood lactates in the cocaine animals is that cocaine affects not only production but clearance as well. If cocaine increases resistance to the mesentery, as shown by Branch and Knuepfer (5), the removal of lactate by the liver could be compromised during cocaine-exercise; however, that explanation is not tenable because those same authors showed that the mesenteric effects of cocaine were reversed by prazosin. If that had been true in the present study, then lactate removal would not have been compromised in our prazosin animals by that mechanism and presumably lactate would have been cleared and accumulation nullified, but that was not the case.

The findings reported here extend the observations of Ojuka et al. (18), who had hypothesized that the effects of cocaine-exercise might be mediated by another catecholamine, epinephrine. This adrenergic hormone is also increased dramatically by cocaine-exercise (9, 10, 12, 14). Epinephrine, even more than norepinephrine, has been known to affect glycogen metabolism by speeding up glycogenolysis (11). To test their hypothesis, Ojuka and coworkers (18) removed the adrenal medulla of rats and exposed them to the cocaine-exercise test. In spite of an absence of epinephrine in the adrenomedullated animals, cocaine-exercise still induced glycogen degradation and lactate accumula-

Table 3. Effects of cocaine on muscle lactate concentration (μmol/g) at rest or exercise with or without prazosin pretreatment (α-1 receptor blockade)

<table>
<thead>
<tr>
<th>Muscle/Condition</th>
<th>S-S (n = 5–6)</th>
<th>P-S (n = 6–8)</th>
<th>S-C (n = 6–9)</th>
<th>P-C (n = 6–10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red vastus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>2.3 ± 0.8</td>
<td>3.1 ± 0.5</td>
<td>2.3 ± 0.6</td>
<td>3.0 ± 0.4</td>
</tr>
<tr>
<td>4-min Ex</td>
<td>2.4 ± 0.9</td>
<td>3.1 ± 0.8</td>
<td>6.1 ± 7.8</td>
<td>7.3 ± 4.4</td>
</tr>
<tr>
<td>15-min Ex</td>
<td>2.4 ± 0.6</td>
<td>2.8 ± 0.9</td>
<td>2.8 ± 0.8</td>
<td>3.3 ± 1.0</td>
</tr>
<tr>
<td>White vastus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>3.4 ± 1.1</td>
<td>3.0 ± 0.9</td>
<td>2.9 ± 0.4</td>
<td>3.5 ± 1.0</td>
</tr>
<tr>
<td>4-min Ex</td>
<td>17.1 ± 10.7</td>
<td>26.9 ± 26.4</td>
<td>31.7 ± 24.5</td>
<td>23.1 ± 15.2</td>
</tr>
<tr>
<td>15-min Ex</td>
<td>2.8 ± 0.4</td>
<td>4.9 ± 1.1</td>
<td>4.2 ± 1.7</td>
<td>3.9 ± 1.7</td>
</tr>
<tr>
<td>S-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>1.5 ± 0.2</td>
<td>1.5 ± 0.4</td>
<td>1.5 ± 0.4</td>
<td>2.3 ± 0.4</td>
</tr>
<tr>
<td>4-min Ex</td>
<td>1.8 ± 0.8</td>
<td>2.4 ± 0.8</td>
<td>4.8 ± 3.9</td>
<td>3.1 ± 1.1</td>
</tr>
<tr>
<td>15-min Ex</td>
<td>2.0 ± 0.7</td>
<td>2.6 ± 0.7</td>
<td>2.6 ± 0.8</td>
<td>3.4 ± 1.1</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of rats/treatment group.
tion. On the basis of those results, Ojuka et al. (18) rejected their hypothesis that the abnormal metabolic effects of cocaine-exercise were mediated by epinephrine.

The precise mechanism by which cocaine exerts its metabolic effects still awaits elucidation. Alternatives have been proposed in the papers by Han et al. (12) and Ojuka and coworkers (18). For instance, Leon-Velarde et al. (16) have shown that cocaine treatment hindered mitochondrial function. If that occurs during exercise, then the muscle would rely less on aerobic systems for energy production and more on anaerobic ATP production with a corresponding accumulation of lactic acid, as we have shown. Cocaine is also known to stimulate calcium release from the sarcoplasmic reticulum (17). Because calcium turns on glycogenolysis (7), this effect could lead to enhanced glycogen degradation during exercise and glycogen wasting. Alternatively, cocaine may alter muscle fiber type recruitment during exercise (18). The observation in the present study and other studies that cocaine causes rapid glycogenolysis in the white vastus lateralis muscle at exercise intensities that, in the absence of cocaine, cause little (9, 14) or no (18) glycogen breakdown, could occur because the drug induces excessive and extraneous recruitment of muscle fibers.

Finally, cocaine could inhibit blood flow to working muscle by reducing cardiac output. Recently, Branch and Knuepfer (5, 6) showed that cocaine administered at a dose similar to that used in the present study decreased cardiac output in conscious rats at rest by 18–30% within 1 min of administration. A decrease in cardiac output of that magnitude during the onset of exercise could severely limit blood flow to working muscle and result in hypoxia, anaerobiosis, glycogen degradation, and lactate accumulation. Those same authors, however, showed that prazosin pretreatment completely reversed the effects of cocaine on cardiac output. This explanation for our observations seems implausible, therefore, because, if cocaine’s effects were mediated through a reduction in cardiac output and prazosin ameliorated that effect, then the elevation of lactate and glycogenolysis should also have been eliminated in the prazosin-treated group, but it was not. However, other effects of prazosin could be confounding the problem. Because prazosin blocks α-1 receptors, it reduces blood pressure, as shown in our pilot project and by others (5), by a general peripheral vasodilation. A general vasodilation during exercise in the prazosin animals would result in a decreased blood flow to the working muscle. Working muscle generally relies on redistribution of blood flow to meet its metabolic needs. Blockage of that redistribution by prazosin would then result in a limited oxygen delivery, a greater anaerobic activity, and subsequent glycogen depletion and lactate formation. This could be occurring in the cocaine-treated animals, even though the fall in cardiac output had been reversed by prazosin. A careful look at the exercise data for the prazosin-saline group shows a clear tendency for this scenario. Although the data are not significantly different, there is a trend for increased glycogen degradation in the white vastus muscle (Table 1) and lactate accumulation in blood (Table 2) and muscle (Table 3) as a result of prazosin treatment alone (P-S), effects similar to those for cocaine-saline (C-S). It is possible, then, that cocaine alone alters cardiac output at the onset of exercise, yielding the metabolic consequences we have routinely reported, and that in the presence of prazosin we see the same metabolic profile but for different reasons, i.e., reduced blood flow to working muscle, due not to reduced cardiac output but to a general vasodilation caused by the selective α-blocker.

The work of Benthem et al. (1) suggests still another possible effect of prazosin. Those authors reported that administration of an α-blocker to exercising rats caused a marked elevation in epinephrine. One could speculate that the elevated epinephrine may cause glycogen wasting (11). Benthem and colleagues (1) reported that carbohydrate use was elevated after α-receptor blockade, as estimated from indirect calorimetry data, but they did not measure muscle glycogen changes directly. However, blood lactate was also elevated, which is in harmony with the trend of the present study. But again we hearken back to the findings of Ojuka et al. (18) that the metabolic disturbances caused by cocaine-exercise persisted in the adrenomedullated rat in spite of the absence of epinephrine.

In summary, the combination of cocaine and exercise results in a reproducible depletion of muscle glycogen and accumulation of blood lactate. We have shown in the present study that the pretreatment of animals with the α-1 receptor antagonist prazosin does not eliminate the cocaine-exercise effect. We have concluded from these findings that the effect of cocaine-exercise challenge is not the result of hypoxic conditions mediated by catecholamine-induced vasoconstriction of the vasculature serving the working muscle, but this conclusion is tentative because of the general vasodilatory or hormonal effects of prazosin and the potential confounding effects on metabolism they might have above and beyond those of cocaine alone.

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