Cocaine administration induces human splenic constriction and altered hematologic parameters

MARC J. KAUFMAN,1,2 ARTHUR J. SIEGEL,3 JACK H. MENDELSON,2 STEPHANIE L. ROSE,1 THELLEA J. KUKES,1 MICHELLE B. SHOLAR,2 SCOTT E. LUKAS,2 AND PERRY F. RENSHAW3

1Brain Imaging Center, 2Alcohol and Drug Abuse Research Center, and 3Department of Medicine, McLean Hospital, Harvard Medical School, Belmont, Massachusetts 02478

Kaufman, Marc J., Arthur J. Siegel, Jack H. Mendelson, Stephanie L. Rose, Thellea J. Kukes, Michelle B. Sholar, Scott E. Lukas, and Perry F. Renshaw. Cocaine administration induces human splenic constriction and altered hematologic parameters. J. Appl. Physiol. 85(4): 1877–1883, 1998.—Cocaine is a potent vasoconstrictor that has been shown to alter hemoglobin, hematocrit, and red blood cell counts in both animals and humans. The present study evaluated whether cocaine administration induces splenic constriction in men and whether spleen-volume changes temporally correlate with altered hematologic parameters. Spleen volume was assessed at baseline and after cocaine administration (0.4 mg/kg) by using magnetic resonance imaging. A group of five healthy men, aged 31 ± 2 (SE) yr and reporting occasional cocaine use (13 ± 5 lifetime exposures), participated. Cocaine reduced spleen volume by 20 ± 4% (P < 0.03) 10 min after drug administration. Spleen volume returned to normal (101 ± 3% baseline) within 35 min after cocaine administration, indicating that the reduction is a transient phenomenon. In subjects administered cocaine from whom blood samples were obtained (n = 3), cocaine increased hemoglobin levels, hematocrit, and red blood cell count to 104.5 ± 0.9, 105.6 ± 1.2, and 106.5 ± 1.0% of baseline levels, respectively (P < 0.03), but it did not alter white blood cell and platelet counts. Placebo administration (n = 5) did not alter hematologic parameters. These results suggest that cocaine induces splenic constriction in humans, and this may contribute to temporally concordant hematologic parameter changes. These events may help to preserve or increase tissue oxygenation in periods of high oxygen demand and/or increased vascular resistance.

spleen: hemoglobin; hematocrit; magnetic resonance imaging; cerebrovascular circulation

COCAINe is a potent sympathomimetic drug and has profound effects on the human cardiac and cerebral vasculature (13, 18, 36). Although much work has focused on cocaine’s effects in these organs, cocaine may have important effects in other tissues. For example, distribution studies after radiolabeled-cocaine administration document very high levels of radioactivity in monkey and rodent spleen (17, 19). Furthermore, post-mortem human spleen has been found to contain high cocaine concentrations after drug overdose (23). Cocaine abuse has been associated with splenic infarction (20) and with abnormal spleen hemodynamics (25). Consequently, the human spleen may also be a target organ for cocaine.

Results from studies in animals suggest that the spleen constricts after cocaine administration. In dogs, cocaine administration increased hemoglobin concentration as well as arterial oxygen content and myocardial oxygen delivery, effects that were abolished by splenectomy (26, 28). These effects may, in part, be mediated by catecholamines acting on the spleen, because norepinephrine infusion in dogs induces splenic constriction, elevated hemoglobin levels, and increased arterial oxygen content (26). Although these studies in dogs are evidence in favor of a splenic response to cocaine, human spleen reactivity to cocaine may be very different. In this regard, although the human spleen is thought to play a role as an erythrocyte reservoir, its limited volume, minimal smooth muscle fiber content, and small contractile response to sympathetic stimulation (1) have been interpreted to suggest that this role is not physiologically important (1).

Yet, recent evidence suggests that acute human cocaine exposures are associated with erythrocytoma, paralleling results cited above in dogs that have been attributed to splenic constriction (26, 28). Specifically, coca leaf (Erythroxylum coca) chewing by humans, a widespread practice in certain Andean populations, has been associated with acutely elevated hemoglobin levels and hematocrit (6, 31). Furthermore, human intranasal and intravenous cocaine administration have been shown to acutely elevate hemoglobin levels and hematocrit (29). The human spleen is capable of constriction, with splenic volume reductions (40–60%) and concomitant hematocrit and/or erythrocyte increases occurring during graded exercise (8, 15). The exercise-induced effect is associated with increased plasma catecholamine levels (15) and has been postulated to occur to provide additional oxygen delivery to tissues during periods of high demand (8, 15).

Together, these findings suggest that the human spleen may constrict in response to cocaine and contribute to temporally concordant hematologic changes. Understanding the mechanisms of physiological control and variation of hemoglobin levels is important because of the role hemoglobin may have in regulating tissue blood flow (32). Accordingly, we used magnetic resonance imaging to evaluate whether cocaine administration caused changes in human spleen volume and whether any such changes were temporally correlated with altered hematologic parameters.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
METHODS

Subjects. Subjects participated in one of two protocols, either a spleen or brain magnetic resonance imaging study. Because menstrual cycle phase in women can modulate the effects of cocaine (12), only men were evaluated in this study. All subjects were studied while they were in the supine position. The spleen-imaging study group consisted of five men who were aged 32 ± 1 (SE) yr and weighed 79 ± 2 kg. This group reported occasional cocaine use (13 ± 5 lifetime exposures, primarily via insufflation). Venous blood samples were obtained from two of these subjects to determine hematologic parameters during spleen imaging. Venous blood samples were also obtained from an additional six men participating in brain imaging studies in which cocaine was administered. The average age and weight of the eight subjects in the latter group were 30 ± 2 yr and 77 ± 3 kg, respectively, and lifetime cocaine use averaged 14 ± 6 exposures, primarily via insufflation. These characteristics are statistically equivalent to those for the group participating in the spleen imaging study. All subjects provided written informed consent to participate in the studies, which were conducted with McLean Hospital Institutional Review Board approval. Subjects underwent a complete physical and neurological examination, including electrocardiogram and blood work before the study. All subjects admitted to the study were judged to be in good health. Immediately before scanning, subjects provided breath and urine samples for the detection of recent alcohol or illicit drug use. Breath samples were analyzed with an Alco Sensor III (Intoximeters, St. Louis, MO), and urine samples were analyzed with a Triage Test (Biosite Diagnostics, San Diego, CA). All subjects tested negative for recent alcohol and illicit substance use.

An 18-gauge angiocatheter was inserted in a vein overlying the antecubital fossa for drug administration. The patency of this intravenous line was checked by bolus infusion of normal saline, and the line was subsequently kept open with 30 ml/h flow of normal saline. Some subjects had an additional catheter (Kowarski-Cormed thromboresistant butterfly catheter) inserted in the opposite antecubital vein for blood sampling to determine venous hematologic parameters and plasma cocaine levels. Subjects were fitted with noninvasive cardiovascular monitoring equipment (In Vivo Research, Orlando, FL), including four-lead electrocardiogram, blood pressure cuff, and pulse oximeter, to provide continuous monitoring throughout the experiment.

Plasma cocaine and venous hemoglobin and hematocrit analyses. Blood samples were collected while subjects were in the supine position, with their arms extended at their sides, and without the use of a tourniquet. Plasma samples were obtained by collecting 3-ml whole-blood samples into tubes containing sodium fluoride, which were placed on ice. Specimens were centrifuged for 10 min, and then plasma was separated and transferred into polypropylene tubes and immediately frozen at −70°C until analysis of cocaine levels. Plasma cocaine levels were measured in duplicate by using a solid-phase extraction procedure on a Hewlett-Packard model 5890 series II gas chromatograph equipped with a capillary column and a Hewlett-Packard series 5971 mass spectrometry detector. The assay sensitivity was 10 ng/ml, and the intra-assay coefficient of variation averaged 1.6% (range 0.2–4.1%). Laboratory personnel were blind with respect to drug treatment condition.

Venous hematologic parameters were determined in serially collected 5-ml venous whole blood samples, which were placed into EDTA tubes. These samples were analyzed with a Mile/Bayer H2 System by a commercial laboratory (Smith-Kline Beecham Clinical Laboratories) for complete blood count and platelet count.

Imaging. Magnetic resonance imaging of the spleen was conducted on a 1.5-T General Electric Signa Scanner by using the body coil. Subjects were placed feet first in the magnet in the supine position for abdominal imaging. Coronal T2-weighted scout images (Fig. 1) were collected with a fast spin-echo pulse sequence. Imaging parameters were as follows: repetition time (TR) = 51 ms, echo time (TE) = 4.2 ms, field of view (FOV) = 48 cm, 5-mm slice thickness with 2.5-mm skip, 256 × 192 matrix, 1 excitation. These images were used to prescribe 16–24 axial slices, extending from the

![Fig. 1. Magnetic resonance imaging of spleen. Top: coronal scout image used to localize spleen. Hatched horizontal line, cross section of spleen documented at bottom. Bottom: axial breath-hold image showing 1 of imaging planes through spleen. Spleen is outlined. Liver (Liv), spleen (S), and kidneys (K) are visible. R, right side of image; L, left side of image.](image-url)
lower abdomen to the region of the middle lung, for spleen-volume measurements. The number of axial slices varied among individuals because of differences in spleen size and positioning. Axial Spoiled Gradient Recalled Acquisition breath-hold images with saturation transfer (Fig. 1) were obtained from these levels with the following parameters: TR = 30 ms, TE = 5 ms, FOV = 32 cm, flip angle = 35°, 128 × 128 or 192 matrix, 4 excitations, and either 5-mm slice thickness and 2-mm skip or (in 1 subject) 8-mm slice thickness and 2-mm skip. Imaging times for each series ranged from 4.5 to 5.5 min. The scan time (i.e., minutes after cocaine administration) was defined as the midpoint of each image series. Scan durations differed between subjects. Consequently, the scan time reported for spleen-volume data was calculated as the average midpoint time of all of the first, second, third, fourth, and fifth postdrug image sets for each of the five subjects. Breath-hold segments ranged from 15 to 22 s per slice, with 5-s breathing intervals between each axial image acquisition. Breath-hold image acquisition was utilized to avoid abdominal motion that would have degraded image quality.

Three baseline image sets were acquired. Then, subjects were administered cocaine (0.4 mg/kg iv) in a single-blind manner via a slow 1-min push. This dose of cocaine was selected because it produces peak plasma cocaine levels comparable to those experienced during intranasal drug administration (35) and is thus physiologically relevant. Five postcocaine image sets were acquired to determine the effects of cocaine on spleen volume. In studies in which placebo was administered (non-spleen-imaging studies), it was done so in a double-blind manner.

Image analysis. For data analysis, all images were transferred to a Sparc10 workstation (SUN Microsystems, Mountain View, CA). Images were analyzed by using software developed by United Medical Systems (Brookline, MA) (11). Images series were randomized for each subject and then analyzed for cross-sectional area by a rater who was blind to the acquisition time (i.e., baseline or postcocaine) of each image series. Total spleen volume was derived by multiplying the cumulative cross-sectional area by the slice plus skip thickness.

Statistical analyses. All data were analyzed with repeated-measures ANOVA.

RESULTS

Cardiovascular measurements. Baseline vital signs were normal in all subjects, with heart rate (HR) averaging 60 ± 2 (SE) beats/min and with systolic (SBP) and diastolic blood (DBP) pressure averaging 132 ± 4 and 65 ± 2 mmHg, respectively. No between-group differences (i.e., subjects in the imaging study vs. those in hematologic parameter study) in baseline cardiovascular parameters were detected. The effects of cocaine and placebo administration on vital signs are shown in Fig. 2. No cocaine-induced differences in HR, SBP, or DBP were detected in a comparison of subjects participating in the spleen-imaging vs. brain-imaging studies (repeated-measures ANOVA). Cocaine significantly increased HR and SBP vs. placebo (P < 0.01 and 0.02, respectively, repeated-measures ANOVA). Dose × time interaction effects were found for HR and SBP (P < 0.001 and 0.03, respectively). Cocaine did not significantly increase DBP compared with placebo (repeated-measures ANOVA).

Spleen-volume measurements. Baseline spleen volume averaged 210 ± 30 (SE) ml. This volume is comparable to human spleen volumes measured with ultrasound (10) and computed tomography (24). The coefficient of variance of within-subject, baseline spleen-volume measurements averaged 7%. After cocaine administration, spleen volume rapidly declined to 80 ± 4% of control values at 10 ± 3 min after cocaine. The spleen-volume reduction was significant (P < 0.03, repeated-measures ANOVA; Fig. 3). Spleen volume gradually returned to baseline (100 ± 3% baseline) within 35 min after cocaine administration (Fig. 3), indicating that this effect is transient.

Hematologic measurements. In subjects participating in blood sampling experiments (n = 8), all baseline hematologic parameters were within normal ranges. Baseline hematocrit averaged 44.2 ± 1.1% and was slightly lower in the three subjects administered co-
caine compared with the five subjects administered placebo (41.6 ± 0.9 vs. 45.8 ± 1.1%; P < 0.05, unpaired t-test). Baseline hemoglobin and red blood cell values averaged 15.0 ± 0.4 g/dl (SE) and 4.8 ± 0.1 × 10^6/mm³, respectively, and were equivalent across experimental groups (i.e., subjects administered cocaine or placebo). Baseline platelet and white blood cell counts averaged 231 ± 12 and 4.5 ± 0.3 × 10³/µl, respectively, and were equivalent across experimental groups.

Cocaine increased hematocrit, hemoglobin, and red blood cell counts to peak values of 105.6 ± 1.2, 104.5 ± 0.9, and 106.5 ± 1.0% of baseline values, respectively, 10–20 min after cocaine administration (Fig. 4). These values all decreased toward baseline levels within 30 min after cocaine. Placebo administration did not alter hematocrit, hemoglobin, or red blood cell counts (Fig. 4). Changes in hematologic parameters were statistically significant as determined with repeated-measures ANOVA. Both a dose and a dose × time interaction effect were found for hematocrit (P < 0.03 and 0.02, respectively), hemoglobin (P < 0.01 and 0.001, respectively), and red blood cell count (P < 0.02 and 0.01), respectively. Cocaine did not significantly alter platelet or white blood cell counts (data not shown).

Plasma cocaine levels were zero at all times in all subjects administered placebo. Peak plasma cocaine levels averaging 200 ± 30 (SE) ng/ml were obtained ~10 min after cocaine administration (Fig. 4). These values declined to approximately one-half of their peak value within 30 min after cocaine administration (Fig. 4).

DISCUSSION

The present data document a transient, cocaine-induced constriction of the human spleen that is temporally concordant with both plasma cocaine levels and hematologic-parameter changes. From this temporal concordance, we infer that cocaine-induced hematologic changes are in part mediated by splenic constriction. Hematologic changes detected from venous blood samples may not exactly reflect arterial blood values, so the exact effect of cocaine on arterial blood hematologic parameters cannot be ascertained by the present data. The present spleen-volume and hematologic changes occurred at plasma cocaine levels that are routinely experienced by intranasal cocaine users (35), suggesting that they may occur frequently in association with illicit cocaine use.

Prior pharmacological characterization of splenic constriction and elevated hemoglobin and hematocrit levels suggests that the present effects may be mediated by splenic α₁-adrenergic receptors (22). Systemic or direct (i.e., into the splenic artery) administration of α₁-adrenergic-receptor agonists or splenic nerve stimulation all induce splenic constriction and hematologic changes (22). This suggests that these effects may be mediated by either peripheral or local catecholamine release. Intravenous cocaine has been shown to elevate circulatory catecholamine levels in dogs (28), whereas oral cocaine administration has been shown to elevate plasma catecholamines in humans (31). Additionally, in humans, plasma norepinephrine and epinephrine levels closely correlate with spleen volume in graded
exercise experiments (15). Consequently, it appears that a cocaine-induced elevation in circulatory catecholamine levels may contribute to cocaine-induced splenic constriction. Local splenic catecholamine release may also contribute, because direct stimulation of the splenic nerve in the presence of cocaine results in greater norepinephrine overflow than at baseline in cats (5). Because cocaine blocks norepinephrine-uptake sites, it could enhance any effects of locally released norepinephrine at splenic α₁-adrenergic receptors.

Although the splenic constriction detected presently was substantial (up to 20%), this degree of volume reduction does not appear to be able to fully account for the temporally concordant changes in hematologic parameters. Following on the theoretical calculations provided by Laub et al. (15), who determined spleen-volume changes and venous hematocrit in humans after graded exercise, we have estimated that cocaine-induced splenic constriction should, at most, account for one-third of the hematocrit rise observed in the present study. Specifically, by using in our subjects a baseline spleen volume of 210 ml, a baseline systemic venous hematocrit of 42, a maximal spleen-volume reduction of 25%, an estimated splenic hematocrit of 80 (15), and a total blood volume of ~5,000 ml, the maximal hematocrit increase expected if the spleen-volume reduction were solely responsible for the effect would be 42.9, or 102% of baseline. However, we observed peak hematocrit, hemoglobin, and red blood cell increases of 105–106% of baseline levels. Furthermore, spleen volume had fully recovered before normalization of hematologic parameters. Thus factors in addition to spleen constriction probably contribute to the hematological alterations associated with cocaine administration, a conclusion paralleling that of Laub et al. The present finding also parallels that of Cabanac et al. (3), who reported that seal splenic constriction could not fully account for hematocrit increases after adrenergic stimulation (3). They noted additional factors that might contribute to hematologic changes, including expulsion into the general circulation of normally sequestered and concentrated red blood cell pools from other organs, such as has been observed in canine liver and intestine, and/or from the inferior vena cava after carotid occlusion or hemorrhage as observed by Carneiro and Donald (4). Additionally, shifts in human abdomen blood radioactivity after graded exercise have been reported (8) and could, if blood is released from concentrated red blood cell pools, contribute to the elevated hemoglobin levels and hematocrit. Furthermore, cocaine is known to evoke pronounced peripheral vasoconstriction (30, 34), and a cocaine-induced reduction in total blood volume that may result from several mechanisms (6) also could contribute to apparent elevations of hematologic parameters. Alternatively, if splenic constriction occurs in a phasic manner, it is conceivable that the present imaging methods, with 5-min acquisition times, failed to detect the maximal extent of spleen constriction. Studies in splenectomized individuals may help to clarify the splenic contribution to cocaine-induced hematologic changes.

Physiological relevance of spleen-volume changes. Cocaine-induced hematologic changes have been termed a "blood-doping" effect of the drug and have been postulated to occur to balance oxygen delivery to cardiac tissue during peak oxygen demand and increased coronary vascular resistance (28). Although the hematologic changes detected presently are small (<6%), particularly when compared with changes observed in dogs administered cocaine (peak hemoglobin increases of 21%) (28), such changes closely parallel those reported in humans administered cocaine orally via coca leaf chewing (6, 31) and are on the order of changes observed in humans during graded-exercise experiments (8, 15). Consequently, a similar blood doping mechanism may be present in humans and may in part be mediated by splenic constriction after cocaine or exercise. In support of this, spleen-volume reductions comparable in magnitude to those observed presently have also been noted in humans during graded-exercise challenges (8, 15). It was postulated that those exercise-induced changes function to redistribute blood from the splanchnic to the cardiovascular system to increase oxygen-carrying capacity during periods of increased oxygen use (8, 15). Autologous erythrocyte infusion results in a nearly linear relationship between percent hemoglobin increase and percent increase in maximal aerobic power (27). Thus a 5% increase in hemoglobin levels, comparable to the increase detected in the present study, induced an ~5% increase in maximal aerobic power. Such an effect might help to compensate for increased coronary and peripheral vascular resistance after cocaine administration and might also reduce physiological strain after cocaine administration. The elevation of plasma catecholamines and/or activation of the sympathetic nervous system may be the common denominator for these seemingly parallel effects of cocaine and exercise. Spleen constriction and hematologic changes are likely a direct result of cocaine. Given the potential importance this effect may have in helping to preserve cardiovascular function and tissue oxygenation, further work appears warranted to more fully characterize the mechanisms underlying hematologic variations induced by cocaine and exercise in humans.

The importance of understanding physiological variations in hemoglobin concentration and hematocrit is further underscored by the recent elucidation that hemoglobin acts as a physiological oxygen gradient sensor, and in doing so it regulates tissue blood flow (32). Consequently, changes in hemoglobin levels and hematocrit may themselves affect hemodynamic function in many tissues. For example, laser Doppler flowmetry measurements are suggestive of abnormally low cerebral blood flow (CBF) in polycythemia vera (7), a myeloproliferative disease associated with abnormally high hemoglobin levels and hematocrit. Hematocrit normalization (~16%) in such patients, accomplished with phlebotomy and myelosuppressive therapy, was accompanied by increased CBF velocities (+20%) in the middle, anterior and posterior cerebral and basilar arteries (7). Conversely, an acute hematocrit increase
(+8%, comparable to the +6% observed presently) during hemodialysis secondary to a blood volume loss has been associated with decreased cerebral blood flow velocity (~20%) in the middle cerebral and basilar arteries (9). Although Doppler flowmetry measurements are subject to inaccuracies associated with hematocrit changes (14), and, although hematocrit increases secondary to dialysis-induced blood volume losses are not physiologically equivalent to those occurring after red blood cell autotransfusions, the apparent inverse relationship between hematocrit and CBF suggests that hematocrit increases associated with cocaine may contribute to cocaine’s global inhibition of CBF (36).

In addition to brain blood flow, human peripheral vascular blood flow is persistently reduced after cocaine, an effect attributed to vasocstriction (30, 34). This peripheral vascular effect could result from an elevation of hemoglobin levels and hematocrit, which in turn might reduce peripheral blood flow in manner analogous to that observed in polycythemia vera. When combined with the vasocnstrictive effects of cocaine, elevated circulatory hemoglobin and hematocrit levels and the possible blood flow reduction they may evoke (28, 30, 34) may predispose certain tissues or regions of tissues with marginal hemodynamic function to experience hypoperfusion or ischemia. Indeed, hypoperfusion and ischemia have been observed in human brain (36) and mesentery (33) in association with cocaine abuse. It is unclear whether any protection from these blood flow abnormalities is conferred by a blood doping effect in tissues other than the heart (28) or whether protection is maintained in humans with histories of chronic cocaine use, whose splicenic function may be abnormal (25).

Hematologic changes may also have bearing on one of the noninvasive magnetic resonance approaches used to examine cerebral function, the blood oxygen level-dependent (BOLD) functional magnetic resonance imaging method, which assumes that the total hemoglobin concentration remains constant (21). Although this assumption is likely to be true in most applications, it is clear from the present data and from prior work (6, 26, 28, 29, 31) that cocaine alters hemoglobin levels and hematocrit. Although cocaine-induced hematologic changes in humans are small in magnitude, and in the present study are smaller than intersubject differences in baseline values, a recent study has documented that the magnitude of hemoglobin change observed presently is sufficient to significantly alter functional magnetic resonance imaging BOLD responses. In that work, a linear relationship between hemoglobin levels and the BOLD response was noted, and a 6% reduction in hemoglobin (accomplished with hemodilution) was associated with a 29% reduction in the BOLD response to photic stimulation (16). Thus it can be anticipated that in studies in which cocaine (2) or other challenges are presented that induce hemoglobin and hematocrit changes, relationships between the magnitude of BOLD signal change and magnitude of focal tissue activation may be more complicated than previously thought.

In summary, the present findings document a cocaine-induced constriction of the human spleen that is temporally concordant with plasma cocaine levels and with hematologic changes. On the basis of theoretical calculations, the degree of cocaine-induced splenic constriction does not appear to be able to fully account for the cocaine-induced increases in hemoglobin levels, hematocrit, and red blood cell concentrations, suggesting that other sequestered, concentrated, red blood cell pools of multiple origins are liberated by cocaine administration. These hematologic changes may help to preserve tissue oxygenation in periods of high oxygen demand and/or increased vascular resistance and may have profound effects on tissue perfusion as well as on the interpretation of functional magnetic resonance imaging BOLD signal changes in cocaine administration studies.

The authors thank Dr. Bruce M. Cohen, Dr. Lawrence L. Wald, Anne M. Smith, and Eileen Connolly for assistance. This work was Supported by National Institute on Drug Abuse Grants DA-09448, DA-0059, DA-00064, DA-00329, and DA-00343. Address for reprint requests: M. J. Kaufman, Brain Imaging Ctr., McLean Hospital, 115 Mill St., Belmont, MA 02478 (E-mail: kauflman@mclean.org).

Received 17 February 1998; accepted in final form 15 June 1998.

REFERENCES


