PET Studies of the Effects of Aerobic Exercise on Human Striatal Dopamine Release

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In vivo microdialysis studies have shown that exercise increases the concentration of dopamine (DA) in the striatum of the rat brain. It has also been shown that PET with [^{11}C]raclopride can be used to assess changes in brain DA induced by drugs and by performance tasks such as playing a video game. The purpose of this study was to evaluate the effects of exercise (treadmill running) on striatal DA release in the human brain. **Methods:** Twelve healthy volunteers (5 women, 7 men; mean age, 32 ± 5 y; age range, 25–40 y) with a history of regular exercise received 2 PET scans with [^{11}C]raclopride on 2 separate days, 1 at baseline and 1 at 5–10 min after running on a treadmill for 30 min. The speed and inclination of the treadmill were increased gradually to reach a maximal speed of 9.7 km/h (6 mph) and a maximal inclination of 10°. Data were acquired on a Siemens HR$^+$ scanner in 3-dimensional mode for 60 min. Heart rates and electrocardiograms were monitored. DA D_2 receptor availability was measured using the ratio of the distribution volume in the putamen to that in the cerebellum, which is a function of the number of available binding sites/dissociation constant. **Results:** The subjects ran at an average speed of 8.7 ± 0.5 km/h (5.4 ± 0.3 mph) and at an inclination of 3.3° ± 2°. The maximum effort of running was maintained for 10–15 min. The heart rates of the subjects were increased by 143% ± 47%. DA D_2 receptor availability in the putamen after treadmill running (4.22 ± 0.34) was no different from that of baseline (4.17 ± 0.29; $P < 0.6$). **Conclusion:** No significant changes in synaptic DA concentration were detected, although the subjects exercised vigorously for 30 min.

Key Words: [^{11}C]raclopride; aerobic exercise; PET; dopamine release

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Dopamine (DA) is a neurotransmitter that is important in regulating brain processes involved with movement. Disease- or drug-induced losses in brain DA lead to movement disorders in which subjects have difficulties with motor activities (*1*). DA is also important in regulating pleasurable responses in the brain (*2*) as well as certain aspects of cognitive function (*3,4*), including attention (*5,6*). In vivo microdialysis studies have shown that exercise increases the concentration of DA in the striatum of the rat brain (*7–9*). However, the effect of exercise on human brain dopaminergic transmission has not been evaluated.

It is possible to measure relative changes in synaptic DA concentration associated with pharmacologic or cognitive interventions using PET. These measurements are done using the DA D_2 radiotracer [^{11}C]raclopride. Raclopride's relative low affinity for the DA D_2 receptor makes it sensitive to competition with endogenous DA (*10*). Because repeated measures of [^{11}C]raclopride binding in the human brain are highly reproducible (*11–14*) under no intervention conditions (baseline), changes in its binding after intervention mostly reflect changes in synaptic DA. Furthermore, simultaneous microdialysis and imaging studies in nonhuman primates have shown a linear relation between the changes in DA induced by psychostimulants as assessed with microdialysis and those obtained using imaging (*15,16*). It has been estimated that a 1% decrease in [^{11}C]raclopride binding reflects an ~8% increase in extracellular endogenous DA (*16*). This strategy has been used to measure changes in DA concentration associated with psychostimulant drug administration (*17–20*). Repeated measures of endogenous DA release with [^{11}C]raclopride and pharmacologic stimulation have been shown to be reproducible (*21*) and sensitive to the effects of age (*17*).

In this study, we extend these measurements to the activation by physiologic stimuli as is the case for exercise. Although no PET study has yet shown the feasibility of this approach for exercise, it has been shown that it is sensitive to changes in attention induced by playing a video game (*22*). Aerobic exercise was chosen as a strategy to change the concentration of DA in the human brain.

MATERIALS AND METHODS

Subjects

Studies were approved by the institutional review board of Brookhaven National Laboratory. Twelve healthy volunteers (5 women, 7 men; mean age, 32 ± 5 y; age range, 25–40 y) with a history of regular exercise (5 ± 3 h/wk) were selected for the study. Subjects with neuropsychiatric illnesses, head trauma with loss of consciousness, past and present history of alcohol or substance abuse (except for caffeine and cigarettes), and medical conditions that may alter cerebral functioning were excluded from the studies.

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Prescan urinalysis ensured the absence of psychoactive drug use. The mean body mass index of the subjects was 23.2 ± 3.6 (range, 17–29). Subjects were instructed to discontinue any over-the-counter medication 1 wk before the scan and not to perform any aerobic exercise 24 h before the PET scan. Informed consent was obtained from each participant after the nature of the experiment was fully explained.

Experimental Design

Two PET scans were obtained with [^{11}C]raclopride for each subject on 2 separate days within 3 wk. The subjects were randomly assigned to have aerobic exercise (jogging) before the first scan (n = 8) and no exercise (baseline) before the second scan. The sequence of aerobic exercise assignment was reversed for the rest of the subjects (n = 4). On the day of exercise, the subjects walked on the treadmill with a speed of 3.2 km/h (2 mph) and 0° elevation for 5 min for warm-up and gradually increased at 1.6 km/h (1 mph) every 2 min until it reached 9.7 km/h (6 mph). At the speed of 9.7 km/h (6 mph), the elevation was increased at 2°/2 min with a maximum elevation of 10°. The subjects were asked repeatedly to rate their subjective perception for levels of fatigue and endurance with an analog verbal scale from 1 (no fatigue) to 10 (total exhaustion). The speed and the elevation of the treadmill were adjusted according to the subject's reports of endurance and fatigue and to the level that subjects could run with maximal capability to the end of the test for a total of 30 min. The pulse rates of the subjects were kept above the recommended target heart rate for submaximal exercise testing using a formula: (220 − age) × 85%. The subject walked at a speed of 3.2 km/h (2 mph) and 0° elevation for 5 min as a cooldown period. The radiotracer was injected 5–10 min later. Electrocardiographic recording and pulse rate were obtained every 15 min for 30 min before exercise and were monitored constantly throughout the course of exercise. Pulse rate was recorded every 2 min from the beginning of exercise for a total of 45 min.

PET Scanning

PET scanning was performed with a Siemens HR$^+$ tomograph (Siemens Medical Systems, Hoffman Estates, IL) (resolution, 4.5 × 4.5 × 4.5 mm; full width half maximum [FWHM], 63 slices). To ensure accurate repositioning of subjects for the second scans, an individually molded head holder was made for each subject. The head of the subject was then positioned in the gantry with the aid of 2 orthogonal laser lines, 1 that was placed at the corner of the canthus and the other parallel to the sagittal plane. Before the emission scan, the subjects underwent a transmission scan for attenuation correction using a ^{68}Ge/^{68}Ga rotating rod source. Catheters were placed in an antecubital vein for radiotracer injection. The PET scans were obtained after intravenous injection of 150–300 MBq (4–8 mCi) [^{11}C]raclopride. A series of 20 emission scans (scans were obtained every minute for the first 10 min, and then 10 5-min scans were obtained for the next 50 min) were obtained from the time of radiotracer injection up to 60 min. Data were acquired in 3-dimensional mode.

Image Analysis

Images obtained with the Siemens HR$^+$ scanner were resliced parallel to the line between the anterior and the posterior commissures (AC–PC line). To increase the signal on each plane we summed contiguous planes, which gave us images with a 4.8-mm FWHM rather than the 2.4-mm FWHM from the original planes. Regions of interest (ROIs) in the striatum and cerebellum were drawn directly on the averaged emission images (summation of images obtained between 10 and 60 min). ROIs for the putamen (3 slices) were obtained bilaterally from the planes where they were best identified. Right and left cerebellar (3 slices) regions were obtained in the 3 planes 1.0 and 1.7 cm below the AC–PC lines (Fig. 1). These regions were then projected into the dynamic images to generate time–activity curves for the striatum and cerebellum. Values for the striatal and cerebellar regions were computed using the weighted average from the different slices where the regions were obtained. The D_2 receptor availability was quantified using the ratio of the distribution volume in striatum to that in cerebellum, which corresponds to the number of available binding sites/dissociation constant (B_{max}'/K_d') +1 and is insensitive to changes in cerebral blood flow (CBF) (*23*).

Statistical Analysis

The maximal heart rate of the subjects during the exercise and measures of B_{max}'/K_d' under exercise conditions were compared with the baseline condition using a paired, 2-tailed *t* test.

RESULTS

The subjects ran at an average speed of 8.7 ± 0.5 km/h (5.4 ± 0.3 mph) at an inclination of 3.3° ± 2°. The maximal effort of running was maintained for 10–15 min. The average total running distance was 4.3 ± 0.3 km (2.7 ± 0.2 miles) (range, 3.7–4.6 km [2.33–2.87 miles]). The maximal heart rates of the subjects were increased by 143% ± 47% ($P < 0.0001$; range, 105%–253%). The average concentra-

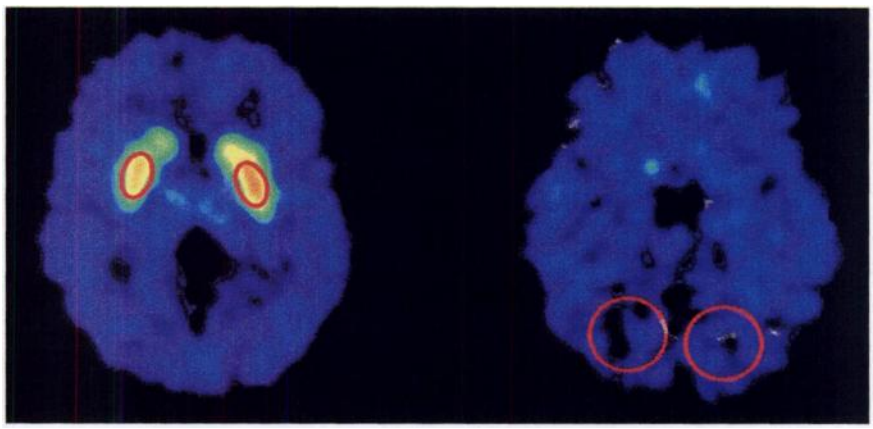

FIGURE 1. Template of ROIs: [^{11}C]raclopride PET images with ROIs at level of cerebellum (left) and putamen (right).

tion of [^{11}C]raclopride in the putamen and cerebellum in the baseline studies was not significantly different from that in the exercise studies (Fig. 2). Nine subjects showed minimal increases or no changes, and 3 subjects showed minimal decreases in DA D_2 receptor availability in the putamen after vigorous treadmill running compared with that of the baseline (Fig. 3). The average DA D_2 receptor availability in the putamen for the 12 subjects after running (4.22 ± 0.34) did not differ from that of the baseline (4.17 ± 0.29; P = 0.6) (Fig. 4).

DISCUSSION

The results of this study do not show changes in striatal [^{11}C]raclopride binding with aerobic exercise. Moreover, the magnitude of B_{max}'/K_d' changes after exercise was within the range of test–retest variability for estimates of DA D_2 receptor availability under baseline conditions as assessed with [^{11}C]raclopride (*11–14*). These findings do not corroborate the results of animal studies documenting increases in extracelluar DA concentration during acute exercise (*7–9*). Failure to observe an effect may reflect the relatively poor sensitivity of the PET raclopride strategy to low levels of DA increase. In fact, microdialysis studies have shown that DA increases a maximum of 80% from baseline (*8*), which is significantly lower than the increases observed after psychostimulant drugs. For example, microdialysis studies for DA have shown increases of 300%–900% after intravenous administration of methylphenidate (2–10 mg/kg) (*24*) and increases of 280%–700% after intravenous administration of cocaine (1–2 mg/kg) (*25,26*). In vivo microdialysis studies on nonhuman primates indicate that an 8% increase in extracellular endogenous DA from amphetamine administration results in a 1% decrease in striatal [^{11}C]raclopride binding (*16*), although one would predict that an 80% increase in extracellular DA from exercise would lead to a 10% decrease in striatal [^{11}C]raclopride binding, which is within the range of the test–retest variability for [^{11}C]raclopride (*11–14*). We had predicted that the raclopride PET method would still detect the increases in DA from exercise because the concentration of DA in the synapse is much higher than that in the extracellular space (*27,28*).

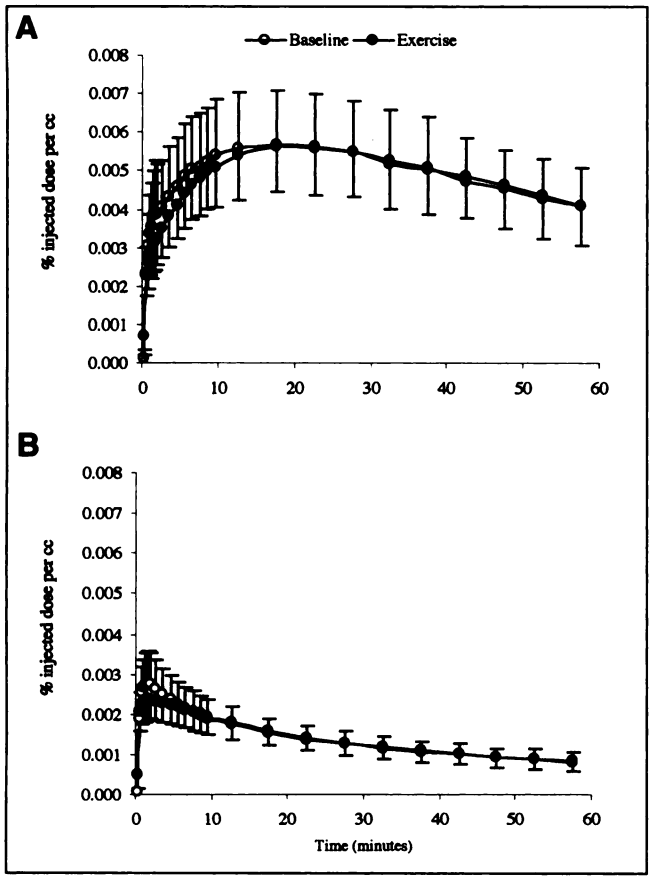

FIGURE 2. Averaged time–activity curves (n = 12) in putamen (A) and cerebellum (B) for baseline (○) and exercise (●) studies.

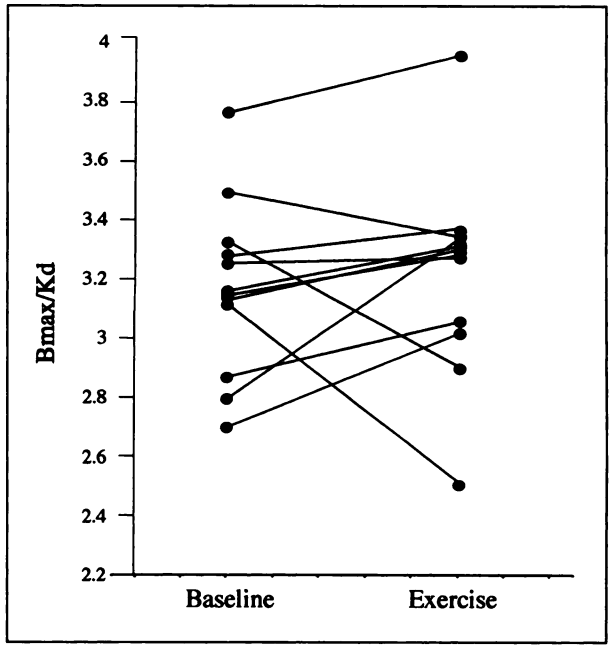

FIGURE 3. Changes in B_{max}'/K_d' between baseline and after aerobic exercise in 12 subjects.

This PET study measured striatal [^{11}C]raclopride binding 10 min after maximal exercise effort, which is different from the animal studies, which measured DA during running and after exercise. Although the animal studies also reported increases in extracelluar DA after exercise, the magnitude of the DA increases was larger during exercise (DA increases of 50%–80% from baseline) than that after exercise (DA increases of 10%–50% from baseline) (*7–9*). Thus, we cannot rule out the possibility that the PET raclopride method may be sensitive to changes in DA if they are measured during exercise. In this respect, this study also differs methodologically from the PET study that documented increases in synaptic DA during a video game in that the [^{11}C]raclopride measures were made while the subject played the video game (*22*), whereas in the current study measures were made when the subjects had finished running. The latter study also used a reinforcement contingent

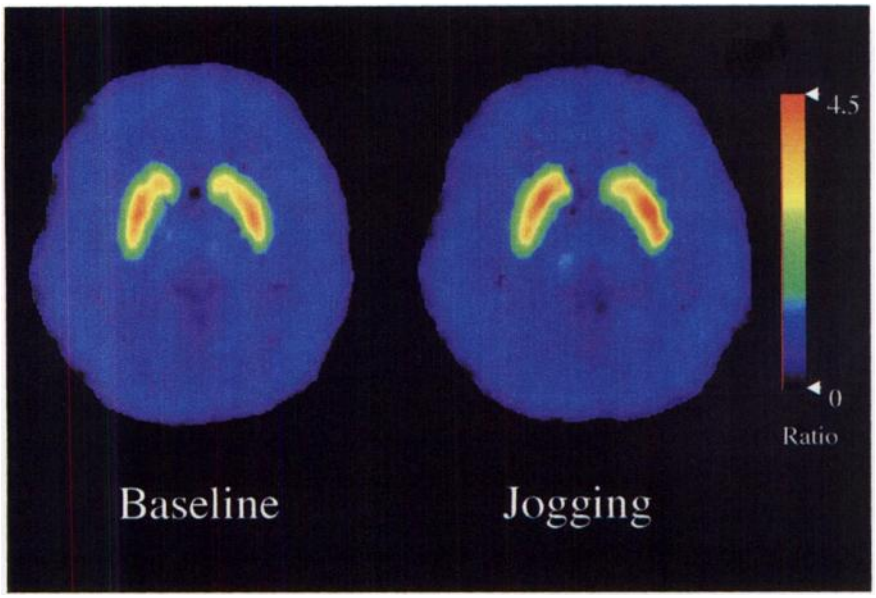

FIGURE 4. Distribution volume ratio images of [^{11}C]raclopride PET studies at level of basal ganglia for baseline and after aerobic exercise. Images for both evaluations are scaled with respect to maximum value obtained on baseline condition and presented using rainbow scale, where red represents highest value (4.5) and dark violet represents lowest value (0).

(subjects were remunerated on the basis of their performance) that may have accounted for the increases in striatal DA because DA is involved in the regulation of reward behavior (*29*).

In this study we recruited only subjects who had a record of regular aerobic exercise to minimize the possibility of exercise-induced complications during the study. Thus, it is possible that the failure to observe an effect could also be associated with the fact that the subjects were chosen to be physically fit, which might have influenced the activity of their striatal DA system. It has been shown that exercise training in animals changes brain DA activity (*9*). Endurance exercise training in laboratory animals has been shown to increase the striatal levels of DA D_2 receptors and of DA metabolism (*30*). The increases in DA D_2 receptors have been shown to persist for up to 2 d after the bout of exercise, and the increases in striatal DA synthesis and monoamine oxidase activity have been shown to persist for up to 7 d of training (*7*). However, it is unclear whether these changes would result in a blunted DA response during exercise in the trained animals, and, though possible, we believe that it is unlikely that we would have detected changes in sedentary individuals.

In vivo microdialysis studies in laboratory animals have shown that the release of DA is influenced by exercise (*7–9*). However, not all studies have been consistent. Whereas some have shown that exercise decreases DA levels in the brain (*31*), others have shown no changes in DA levels but increases in its metabolite, dihydroxyphenylacetic acid (DOPAC), in the striatum (*32*), and still others have shown increases in DA and DOPAC levels in the striatum (*33,34*). Although the discrepancies might be related to differences in the methods used (*35*), the bottom line is that the effects of exercise on DA neurotransmission are unclear. Further studies using more sensitive in vivo quantitative instruments or methods (or both) may help to better elucidate the effects of exercise on DA neurotransmission in the human brain.

One methodologic aspect of this study that is worth mentioning is the influence of CBF in the model parameters used to quantitate [^{11}C]raclopride binding because exercise is likely to change CBF (*36,37*). Although the transport constants K1 and k2 for [^{11}C]raclopride are functions of capillary permeability, plasma protein binding, and CBF, the distribution volume is not dependent on CBF (*23*). Thus, the model parameter used to quantitate changes in striatal DA (B_{max}'/K_d') should have been insensitive to exercise-induced changes in CBF. Also, this study followed a random-order design to control for the potential effect of order. There were no differences between the subjects tested first with exercise and those tested first with no exercise.

CONCLUSION

Even though the subjects ran vigorously on the treadmill for 30 min, we did not detect significant changes in the striatal [^{11}C]raclopride binding compared with the baseline scan. This study suggests that this level of exercise does not induce changes in striatal DA release that are large enough to be detected with the PET raclopride method.

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