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 incline of 10°. Data were acquired on a Siemens HR+ scanner in 3-dimensional mode for 60 min. Heart rates and electrocardiograms were monitored. DA D2 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 D2 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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**D**opamine (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 D2 radiotracer \(^{11}C\)raclopride. Raclopride’s relative low affinity for the DA D2 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.
Prescan urination 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 discontinu...
tion of [11C]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 D2 receptor availability in the putamen after vigorous treadmill running compared with that of the baseline (Fig. 3). The average DA D2 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 [11C]raclopride binding with aerobic exercise. Moreover, the magnitude of $B_{\text{max}}'/K_d'$ changes after exercise was within the range of test–retest variability for estimates of DA D2 receptor availability under baseline conditions as assessed with [11C]raclopride (11–14). These findings do not corroborate the results of animal studies documenting increases in extracellular 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 psycho- 

![FIGURE 3. Changes in $B_{\text{max}}'/K_d'$ between baseline and after aerobic exercise in 12 subjects.](image)

![FIGURE 2. Averaged time–activity curves (n = 12) in putamen (A) and cerebellum (B) for baseline (○) and exercise (●) studies.](image)
(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 D2 receptors and of DA metabolism (30). The increases in DA D2 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 [11C]raclopride binding because exercise is likely to change CBF (36,37). Although the transport constants K1 and k2 for [11C]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 (Bmax/Kd) 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 [11C]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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