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Operantly Conditioned Running: Effects on Brain Catecholamine Concentrations and Receptor Densities in the Rat[1]

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DE CASTRO, J. M. AND G. DUNCAN. *Operantly conditioned running: Effects on brain catecholamine concentrations and receptor densities in the rat.* PHARMACOL BIOCHEM BEHAV **23**(4) 495–500, 1985.—It was hypothesized that endurance exercise results in an alteration in the brain monoamine systems. Rats were trained to run for food reinforcement on a variable ratio schedule in running wheels. Yoked control rats were also allowed to run but were not specifically reinforced for running. The animals ran 5 days per week for 8 weeks and were sacrificed 48 hours after the last endurance training session. The brains were assayed for norepinephrine and dopamine concentrations and β-adrenergic (^{3}H-dihydroalprenolol binding) and dopaminergic (^{3}H-spiroperidol binding) receptor densities. Changes in norepinephrine concentration and β-adrenergic receptor densities were not significantly different between reinforced running and yoked control groups. Dopamine concentrations were significantly higher while dopamine receptor densities were significantly lower in the reinforced running group. These results suggest that chronic running elevates dopamine secretion and consequently produces a compensatory down-regulation of dopaminergic receptor sites. The relationship of these changes to motor activity and to the antidepressant effects of exercise are discussed.

Running Adrenergic receptors Norepinephrine Dopamine/Receptors Dopamine Exercise

EXERCISE has well documented positive physiological benefits (see [18]). There also appears to be positive psychological benefits of aerobic exercise, including relief of anxiety and depression, improvements in self concept and work behavior (see [12, 21, 34] for review). It has been suggested that exercise exerts its putative psychological effect via the same neurochemical substrate (the monoamines) as the antidepressant drugs and electroconvulsive shock therapy (ECT) [34]. Most antidepressant drugs, but not all [43], reduce brain norepinephrine levels when administered acutely, while chronic administration results in compensatory responses which normalize the levels of brain norepinephrine [14,35]. Similarly, acute bouts of exercise result in a depletion of brain norepinephrine [5, 25, 30] while chronic exercise has been found to elevate brain norepinephrine levels [10,11]. Chronic administration of antidepressant drugs and ECT results in a marked reduction in the number of β-noradrenergic receptor sites in the rat brain [4, 6, 7, 14, 17, 35, 36, 38, 41, 46]. It is not known whether chronic exercise induces a similar change. It was thus a goal of the present study to assess the effect of chronic endurance training on brain norepinephrine and β-noradrenergic receptor concentrations.

The dopamine systems of the brain appear to be involved in motor behavior [22, 23, 37, 40] and acute exercise bouts can affect the amount of dopamine found in the rat brain [41] and increase brain dopamine metabolism [8]. At present there are no data on the effect of chronic endurance exercise on the brain dopamine systems. Thus a second goal of the present experiment was to assess the effect of chronic endurance training on rat brain dopamine and dopamine receptor concentrations.

The methods that investigators currently use to induce physical activity in rats are poor models of the ways used in endurance training programs in man. There are three principle weaknesses with current methodologies. First, these techniques place an inappropriate level of stress on the animal, and this could account for the neurochemical effects rather than the exercise. Typically, rats are forced to swim to exhaustion [5,30] or are forced to run on a treadmill to avoid footshock. Acute stress such as this has been shown to reduce brain norepinephrine levels [2, 9, 26, 29, 33, 44] while chronic stress results in normal brain norepinephrine levels [45] and a reduced number of brain noradrenergic receptor sites in response to immobilization stress [42] but not REM deprivation [1]. This pattern of results produced by stress is similar to those reported for exercise. Hence, current methodologies confound exercise and stress effects. In order to observe the effects of the exercise per se, stressers other than those directly related to the exercise itself must be minimized.

A second weakness of the animal model of endurance

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training is that the animal cannot self regulate the duration or intensity of the exercise. Humans typically adjust the intensity and duration of their exercise based upon feedback from the state of their muscular, cardiovascular and respiratory systems, adapting the exercise to their own level of conditioning and their immediate state. This maximizes benefit while minimizing stress. The third weakness with current methodologies is that exercised animals are compared to extremely sedentary controls who have typically been confined to small cages with no opportunity for even a modicum of exercise. The effects seen, then, could be due to the deleterious effects of sedentariness rather than the positive effects of endurance training.

These weaknesses can be overcome by the employment of operant conditioning techniques, using positive reinforcement to induce exercise. The animal can then self-regulate the exercise and not be exposed to excessively stressful conditions or noxious stimuli. Additonally, a yoked control group design can be employed wherein control animals are afforded the opportunity to exercise but are not reinforced for it, thus eliminating enforced sedentariness. Such a system has been employed successfully [28]. The present experiment attempted to assess the effect of chronic endurance training induced via operant techniques, on brain norepinephrine, β-noradrenergic receptor, dopamine and dopamine receptor concentrations in the rat.

METHOD

Animals

Eighteen male Long-Evans hooded rats obtained from the Charles River Breeding Labs weighing between 290 and 370 grams served as subjects. They were housed throughout the experiment in groups of 3 in the colony room with lights off from 2300 to 700 hours. Water was available ad lib throughout the experiment. The animals were paired on the basis of body weight and were then randomly assigned to either experimental or yoked control groups.

Apparatus

Training was conducted in 6 modified Wahman LC34 running wheels (Wahman Manufacturing Co.). A microswitch was attached such that it was closed by each revolution of the wheel. A food cup was mounted inside and a pellet dispenser (Lafayette Instruments Model 80200) was mounted outside of the housing cage ($25 \times 15 \times 13$ cm) attached to the wheel. The microswitches and pellet dispensers were interfaced to an Interdata 6/16 minicomputer which was programmed to record the wheel revolutions and dispense 45 mg food pellets (BioServ, Inc. Product No. 0021). Three of the wheels were designated as experimental (reinforced running) cages and 3 as yoked control cages. The computer was programmed to dispense a food pellet for running in the experimental wheels on a variable ratio schedule and stimultaneously and non-contingently dispense a pellet into the yoked control cages. Wheel revolutions in the yoked control cages were simply recorded and no food was dispensed contingent upon running.

Assay—General

Forty-eight hours after the final endurance training session the animals were sacrificed by decapitation, and the brains were rapidly removed, cut longitudinally into left and right halves and frozen on dry ice. The left or right half was then assigned randomly to either the catecholamine assay or the receptor binding assay with the exception that each yoked pair have the same side assayed with the same procedure.

Assay—Catecholamine Concentrations

The brains were homogenized in 10 ml/gram of 0.4 N perchloric acid containing 5 mM reduced glutathione and centrifuged at 1000 g for 30 minutes at 0°C. The protein free supernatant was collected, diluted 20:1 with distilled water, and assayed for norepinephrine/dopamine concentration using a modification of the radioenzymatic assay technique of Passon and Peuler [32] (Cat-A-Kit, the Upjohn Company). The enzyme COMT is used to catalyze the transfer of a ^{3}H-methyl group to the catecholamines. The resulting products were then isolated by thin layer chromatography and the radioactivity attributable to each catecholamine was determined by scintillation counting.

Assay—Receptor Binding

The brains were homogenized in 20 ml/g of 40 mM tris buffer (adjusted to pH 7.4) and centrifuged at 48,000 g for 30 minutes. The resultant pellet was then resuspended in 20 ml/g tris buffer and centrifuged again at 48,000 g for 15 minutes. The pellet was then diluted with tris buffer to yield a concentration of 10 mg/ml. Triplicate determinations of total and non-specific binding were made at five different concentrations of tritiated ligands (0.4 nM, 1 nM, 2 nM, 4 nM, and 10 nM). Non-specific binding was determined by incubating the suspensions with 1 μM of unlabeled competitor compound. Specific binding at each concentration of tritiated ligand was determined by subtracting the non-specific binding from the total binding. For β-noradrenergic receptor determination ^{3}H-dihydroalprenolol (New England Nuclear) was used as the labeled ligand while l-alprenolol-d-tartrate (Sigma) was used as the unlabeled competitor [13]. For dopamine receptor determination ^{3}H-spiroperidol (New England Nuclear) and Haloperidol (McNeil Pharmaceutical) were used as labeled ligand and unlabeled competitor, respectively [20]. Bound tritiated ligand was then separated from unbound drug by filtration (Whatman GF/B glass microfiber filters), dissolved in scintillation cocktail, and radioactivity determined by scintillation counting. The number of receptors (B_{max}) and their affinities (K_D) were estimated by the method of Zivin and Waud [48] uncorrected for bias.

Procedure

The animals were food deprived for 23 hours and then adapted to the apparatus by placing them individually in the housing cage with the wheel closed for a 2-hour period with the food cup filled with 45 mg food pellets. No formal shaping was performed. The day following adaptation the animals were allowed to discover the running food contingency in a single 24-hour session. The rats were deprived of food for 23 hours, placed in the appropriate (experimental or yoked) wheel, and were reinforced for every revolution in the wheel (CRF schedule) for 3 hours. The schedule was then changed to a variable ratio-4 (VR-4) for 4 hours. If the rat was running considerably and all reinforcers were ingested, the contingency was increased to VR-8 for the remainder of the 24 hours; otherwise VR-4 was maintained. For 3 yoked pairs, a second 24 hour session was run because it was observed that these rats rather than running were

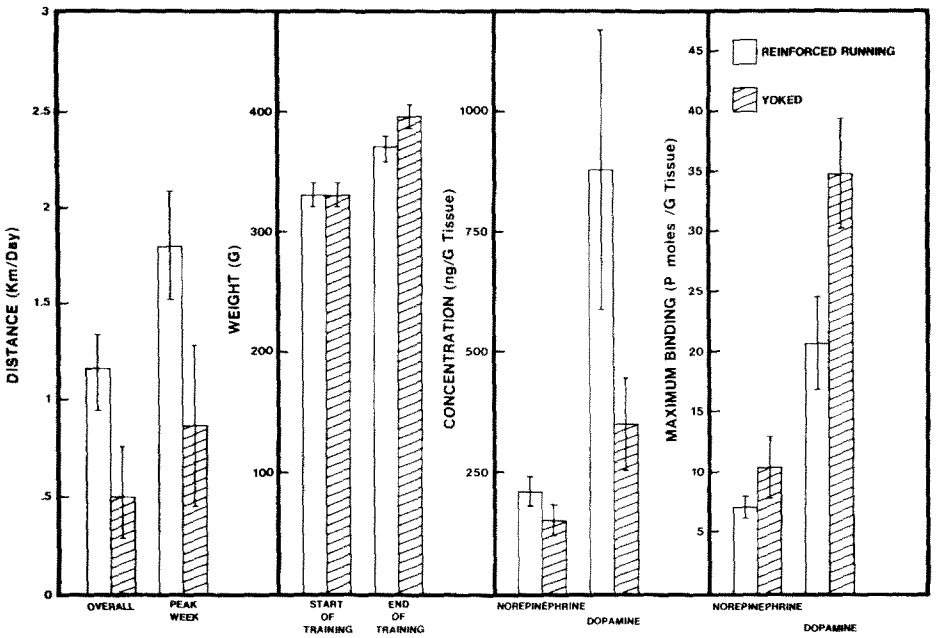

FIG. 1. Mean (±S.E.M.) distance run per day (left panel), body weight (left center panel), catecholamine concentrations (right center panel), and ligand binding (right panel) for the reinforced running (white) and yoked control rats (hatched).

standing in the housing cage and spinning the wheel with their forepaws. The wheel tension was increased to prevent this behavior and the rats reshaped.

For the next 8 weeks the rats were run 5 days per week in 3 squads of 6 rats, 3 experimental and 3 yoked, at 1045, 1300 and 1515 for the 3 squads, respectively. Each day the rats were food deprived for 20 hours, were given a 2 hour reinforced running session, and then were allowed ad lib food for 2 hours. All food intake was measured and body weights recorded before and after each component of the schedule. Water was available ad lib throughout. Over the weekends the rats were given ad lib food and water.

The density of reinforcement was adjusted in order to maximize the amount of running. During the first week the schedule was set as a VR-8. During subsequent weeks the ratio was increased individually until a ratio strain was observed (a significant reduction in the amount of running) in which case the ratio was decreased until a stable rate of responding occurred. Terminal schedule densities varied between VR-16 to VR-36 for different yoked pairs averaging VR-28.

RESULTS

Due to technical problems, no receptor binding data were obtained for three animals, resulting in two of the nine original yoked pairs being dropped from the analysis. A third yoked pair was also dropped since both animals ran only a negligible amount. The following results, then, are for the remaining 12 animals (6 pairs).

The principal results are summarized in Fig. 1. The reinforced running group ran more than twice as far as the yoked control group, both over the entire experiment, $t(5) = 4.18, p<0.01$, and for their maximum running week, $t(5) = 4.06, p<0.01$. The reinforcement contingency, then, was effective in promoting heightened levels of physical exertion. The animals did not significantly differ in body weight either at the beginning, $t(5)=0$ or at the end, $t(5)=1.63$, $p>0.10$ of the experiment, and the amount of food ingested by the two groups did not significantly differ, $t(5) = 1.01$, $p>0.10$.

Whole brain catecholamine concentrations were significantly higher in the reinforced running group than in the yoked controls, $F(1,5) = 10.01$, $p<0.05$. This difference, however, was only significant for the dopamine concentrations, $t(5) = -2.68$, $p<0.05$, and not for the norepinephrine concentrations, $t(5) = 1.69$, $p>0.10$. Since the interaction term in the analysis of variance was not significant, $F(1,5) = 4.77$, $p<0.10$, it cannot be concluded that the exercise treatment differentially affected the two catecholamines.

Receptor affinities ($K_D = 3.99$ nM for ^{3}H-Spiroperidol and 2.63 nM for ^{3}H-dihydroalprenolol binding) were not found to differ between groups, however, whole brain catecholamine maximum receptor binding (B_{max}) was significantly lower in the reinforced running group than in their yoked controls, $F(1,5) = 16.75$, $p<0.01$, and the two catecholamine receptor types were differentially affected, $F(1,5) = 25.64$, $p<0.005$. Maximum ^{3}H-spiroperidol binding was significantly lower in the reinforced running group, $t(5) = 8.90$, $p<0.001$, than in the yoked control group while the maximum ^{3}H-dihydroalprenolol binding was not significantly different, $t(5) = 1.65$, $p>0.10$. The amount of running during the study was positively related to the maximum ^{3}H-spiroperidol binding for both the reinforced running group, $r(5) = .86$, $p<0.05$, and for the yoked control group, $r(5) = .95$, $p<0.01$. The individual data as well as regression lines are presented in Fig. 2. The relationships between amount of running and brain dopamine concentrations, norepinephrine concentrations, or maximum ^{3}H-dihydroalprenolol bindings were not significant.

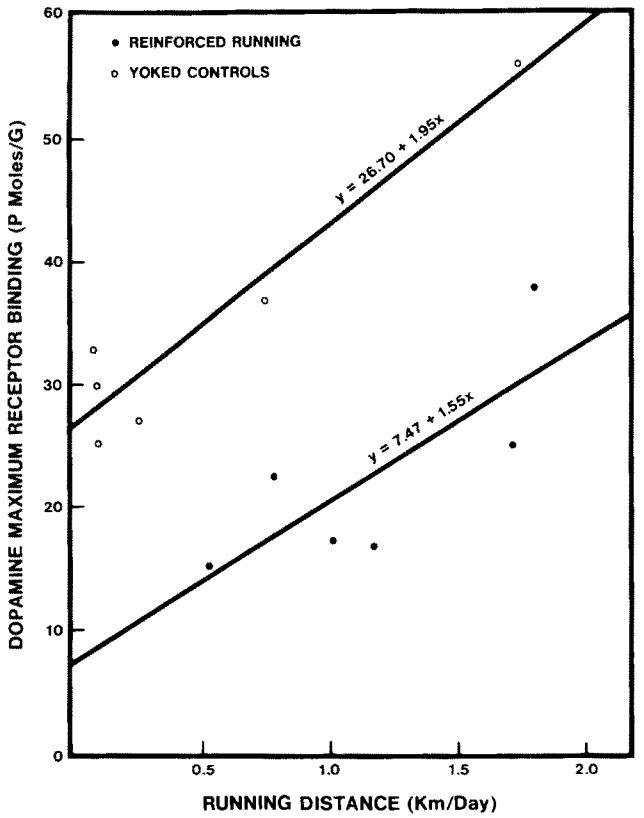

FIG. 2. Individual animal data points and group regression lines for maximum ^{3}H-spiroperidol binding as a function of the mean distance run per day over the entire training period for reinforced running (solid) and yoked control rats (open circles).

DISCUSSION

The present study demonstrated that operant conditioning can be successfully employed to produce a rat model of human exercise. Without shock stress and with self-regulated intensity high levels of running activity could be produced and maintained. Additionally, the yoked control group design resulted in control animals who were not at all sedentary. Hence, the reported effects on neurochemistry could not be due to excess stress unrelated to the exercise or to the debilitating effects of sedentariness, but only to heightened levels of physical activity. It should be noted that the rats were run food deprived and were given food during the exercise. This is quite different from typical human aerobic activity and may be critical for producing the observed neurochemical changes. However, the fact that similar changes are found under shock motivated running conditions [10,11] and that the yoked control rats were also food deprived and fed similarly argues against such an interpretation.

There were no statistically significant effects of running on either norepinephrine concentration or receptor densities. However, previous research has reported a 22% elevation of norepinephrine concentration with forced exercise [10,11]. In the present study the means for norepinephrine concentrations for the reinforced running group was 40% higher, albeit not statistically significant, than for the controls. The lack of a statistically significant effect in the present study may be due to the fact that the control animals were not sedentary, as in previous studies, and this increased the variance within the control group. Indeed, the control animal that ran the most, more than all but one of the reinforced animals, had a brain norepinephrine concentration of 276 pg/g which was higher than all but one of the reinforced running animals.

The lack of a significant effect of exercise on β-adrenergic receptor binding may have occurred for similar reasons. Additionally, U'Prichard and Kvetnansky [42] found that the significant reduction in β-adrenergic receptor binding which results from chronic immobilization stress is reversed if 24 hours are allowed to elapse prior to sacrifice. The lack of a significant effect in the present study, then, may be due to the 2-day delay between the last running session and sacrifice of the animals. Additionally, the use of whole brain homogenates may have been in part responsible for the lack of a significant effect on the adrenergic system. Alterations in norepinephrine and β-adrenergic receptor concentrations resulting from endurance exercise may be regionally specific and these small differences may have been overwhelmed by the mass of unaffected tissue included in the assayed samples.

The use of whole brain homogenates may have resulted in the inclusion of ^{3}H-spiroperidol binding sites other than dopamine receptors such as the 5-HT_2 receptor. The relatively high value of K_D obtained in the present study may be evidence for such a contamination. Caution then must be exercised in interpreting the present findings as a change solely in dopamine receptor binding. A more specific regional determination could result in different findings. Indeed in a recent experiment Gilliam *et al.* [24] found an increased number of ^{3}H-spiperone binding sites in the striatum after endurance training in rats. In this study, however, dopamine concentrations were not measured and only one ligand concentration was used. Additionally, the exercise was more intense than in the present study and was experimenter imposed rather than self-initiated. It is thus unclear whether the regional specificity or these other procedural differences are responsible for the differing results.

The present experiment clearly demonstrates a profound effect of reinforced running on the brain dopamine system; more than doubling the whole brain dopamine content in reference to the yoked control animals. These results probably resulted from the fact that the dopamine system of the brain is involved in motor behavior [22, 23, 40]. The finding in the present study that, within groups, dopamine receptor densities are correlated with the amount of running also supports the notion of dopamine involvement in motor control. The animals' propensity to run was found to be related to the number of dopamine receptors as reflected in ^{3}H-spiroperidol binding. A further increase in the amount of running produced by the reinforcement contingency resulted in a down-regulation of receptors. Recently, Yamamoto and Freed [47] found that operantly conditioning a rat to circle results in an increase in the dopamine, tyrosine hydroxylase, and dihydroxyphenylacetic acid concentration of the contralateral striatum only, demonstrating that motor behavior results in a correlated release of dopamine. Hence, the present results may have occurred due to the associated release of dopamine and motor behavior and a subsequent increase in the rate of dopamine synthesis. The elevated brain dopamine concentrations found are likely due to the 48 hour delay between the last exercise session and sacrificing the animals. The elevated synthesis rate without the exercise-induced increase in utilization would be expected

to yield an excess of brain dopamine. The exercise-induced increase in release would be expected to induce a compensatory down-regulation of dopamine receptor sites.

The significant alteration in the dopamine system may be a structural change related to the putative psychological effects of exercise. Antidepressant drugs and ECS have been shown to reduce the sensitivity of dopamine autoreceptors [15,16] and some antidepressants decrease dopamine receptor densities [27]. The heightened dopamine activity resulting from running as seen in the present results would be expected to result in an overstimulation and a resultant down-regulation of autoreceptor activity. This then may be the structural change responsible for the psychological effects of exercise.

It is not unreasonable to postulate that the addictive qualities of endurance exercise [31,39] are a consequence of the down regulation of dopamine receptor sites. The repetitive overstimulation of the dopamine system produced by exercise is compensated for by the down-regulation of receptor sites which reduces sensitivity. The organism, then, must engage in the endurance activity in order to continue to drive an insensitive receptive structure up to relatively normal levels. Thus, exercise addiction may be viewed as an avoidance response to the negative effects of exercise termination. Such negative withdrawal effects occur with antidepressant drug treatment termination [3]. Additionally there is an inordinately high relapse rate when human depressives in remission are switched from antidepressants to placebos [19]. Whether antidepressant and exercise withdrawal effects result from the same structural basis might be addressed in future research by investigating whether these two treatments have additive effects on depression and withdrawal symptoms.

Regardless of the merits of these speculations, the present study has demonstrated that a rat model of human endurance exercise can be produced without undue stress and with a nonsedentary control. It has also shown that chronic endurance exercise produces lasting (at least 48 hours) changes in the dopamine system, increasing the whole brain content of dopamine while reducing dopamine receptor binding.

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REFERENCES

1. Abel, M. S., F. Villegas, J. Abreu, F. Gimino, S. Steiner, B. Beer and C. R. Meyerson. The effect of rapid eye movement sleep deprivation on cortical β-adrenergic receptors. *Brain Res Bull* **11:** 729-734, 1983.
2. Anisman, H. and L. S. Sklar. Catecholamine depletion in mice upon reexposure to stress: Mediation of the escape deficits produced by inescapable shock. *J Comp Physiol Psychol* **93:** 610-625, 1979.
3. Baldessarini, R. J. Drugs and the treatment of psychiatric disorders. In: *The Pharmacological Basis of Therapeutics*, edited by A. G. Gilman and A. Gilman. New York: MacMillan, 1980, pp. 391-447.
4. Banerjee, S. P., L. S. Kung, S. J. Riggi and S. K. Chanda. Development of β adrenergic receptor subsensitivity by antidepressants. *Nature* **268:** 455-456, 1977.
5. Barchas, J. D. and D. X. Freedman. Brain amines: response to physiological stress. *Biochem Pharmacol* **12:** 1232-1235, 1963.
6. Bergstrom, D. A. and K. J. Kellar. Effect of electroconvulsive shock on monaminergic receptor binding sites in rat brain. *Nature* **278:** 464-466, 1979.
7. Bergstrom, D. A. and K. J. Kellar. Adrenergic and serotonergic receptor binding in rat brain after chronic desmethylimipramine treatment. *J Pharmacol Exp Ther* **209:** 256-261, 1979.
8. Bliss, E. L. and J. Ailion. Relationship of stress and activity to brain dopamine and homovanillic acid. *Life Sci* **10:** 1161-1169, 1971.
9. Bliss, E. L. and J. Zwanziger. Brain amines and emotional stress. *J Psychiatr Res* **4:** 189-198, 1966.
10. Brown, B. S., T. Payne, C. Kim, G. Moore, P. Krebs and W. Martin. Chronic response of rat brain norepinephrine and serotonin levels to endurance training. *J Appl Physiol* **46:** 19-23, 1979.
11. Brown, B. S. and W. Van Huss. Exercise and rat brain catecholamines. *J Appl Physiol* **34:** 664-669, 1973.
12. Brown, R. S., D. E. Ramiriz and J. M. Taub. The prescription of exercise for depression. *Phys Sportsmed* **6:** 35-45, 1978.
13. Bylund, D. B. and S. H. Snyder. Beta-adrenergic receptor binding in membrane preparations from mammalian brain. *Mol Pharmacol* **12:** 568-580, 1976.
14. Campbell, I. C., D. S. Robinson, W. Lovenberg and D. L. Murphy. The effects of chronic regimens of clorgyline and pargyline on monoamine metabolism in the rat brain. *J Neurochem* **32:** 49-55, 1979.
15. Chiodo, L. A. and S. M. Antelman. Repeated tricyclics induce a progressive dopamine autoreceptor subsensitivity independent of daily drug treatment. *Nature* **287:** 451-454, 1980.
16. Chiodo, L. A. and S. M. Antelman. Electroconvulsive shock: Progressive dopamine autoreceptor subsensitivity independent of repeated treatment. *Science* **210:** 799-801, 1980.
17. Cohen, R. M., I. C. Campbell, M. Dauphin, J. F. Tallman and D. L. Murphy. Changes in α and β receptor densities in rat brain as a result of treatment with monoamine oxidase inhibiting antidepressants. *Neuropharmacology* **21:** 293-298, 1982.
18. Collingwood, T. HRD model and fitness. In: *Human Resource Development Model in Education*, edited by D. Kratochvil. Baton Rouge, LA: Southern University Press, 1973, pp. 143-188.
19. Coppen, A. and M. Peet. The long-term management of patients with affective disorders. In: *Psychopharmacology of Affective Disorders*, edited by E. S. Paykel and A. Coppen. New York: Oxford University Press, 1979, pp. 248-256.
20. Fields, J. Z., T. O. Reisine and H. I. Yamamura. Biochemical demonstration of dopaminergic receptors in rat and human brain using ^{3}H-spiroperidol. *Brain Res* **136:** 578-584, 1977.
21. Folkins, C. H. and W. E. Sine. Physical fitness training and mental health. *Am Psychol* **36:** 373-389, 1981.
22. Fujita, N., H. Akira, K. Saito and H. Yoshida. Multiple postsynaptic dopamine receptors and behavioral manifestations. *Pharmacol Biochem Behav* **16:** 437-440, 1982.
23. Gershanik, O. S., R. E. Heikkila, R. C. Duvoisin and L. Manzino. Behavioral correlates of dopamine receptor interaction. *Neurology* **32:** A161, 1982.
24. Gilliam, P. E., W. W. Spirduso, T. P. Martin, T. J. Walters, R. E. Wilcox and R. P. Farrar. The effect of exercise training on ^{3}H-spiperone binding in rat striatum. *Pharmacol Biochem Behav* **20:** 863-867, 1984.

25. Gordon, R., S. Spector, A. Sjoerdsma and S. Udenfriend. Increased synthesis of norepinephrine and epinephrine in the intact rat during exercise and exposure to cold. *J Pharmacol Exp Ther* **153:** 440-447, 1966.
26. Keim, K. L. and E. B. Sigg. Physiological and biochemical concomitants of restraint stress in rats. *Pharmacol Biochem Behav* **4:** 289-297, 1976.
27. Koide, T. and H. Matsushita. An enhanced sensitivity of muscarinic cholinergic receptor associated with dopaminergic receptor subsensitivity after chronic antidepressant treatment. *Life Sci* **28:** 1139-1145, 1981.
28. Massaro, F. and M. A. McCamish. A behavioral model for quantifying physiologic adjustments of food intake and body composition to exercise in rats. *Am J Clin Nutr* **35:** R29, 1982.
29. Maynert, E. W. and R. Levin. Stress-induced release of brain norepinephrine and its inhibition by drugs. *J Pharmacol Exp Ther* **143:** 90-95, 1964.
30. Moore, K. E. and E. W. Laviviere. Effects of d-amphetamine and restraint on the content of norepinephrine and dopamine in rat brain. *Biochem Pharmacol* **12:** 1283-1288, 1963.
31. Morgan, W. P. Negative addiction in runners. *Phys Sportsmed* **7:** 57-70, 1979.
32. Passon, P. G. and J. D. Peuler. A simplified radiometric assay for plasma norepinephrine and epinephrine. *Anal Biochem* **51:** 618-631, 1973.
33. Paulsen, E. C. and S. M. Hess. The rate of synthesis of catecholamines following depletion in guinea pig brain and heart. *J Neurochem* **10:** 453-459, 1963.
34. Ransford, C. P. A role for amines in the antidepressant effect of exercise: a review. *Med Sci Sports Exerc* **14:** 1-10, 1982.
35. Robinson, D. S., I. C. Campbell, M. Walker, N. J. Statham, W. Lovenberg and D. L. Murphy. Effect of chronic monoamine oxidase inhibitor treatment on biogenic amine metabolism in the rat bain. *Neuropharmacology* **18:** 771-776, 1979.
36. Sellinger, M., K. Sarai, A. Frazer, J. Mendels and M. E. Hess. Beta adrenergic receptor binding in rat cerebral cortex after repeated administration of psychotropic drugs. *Fed Proc* **37:** 309, 1978.
37. Simpson, B. A. and S. D. Iverson. Effects of substantia nigra lesions on the locomotor and stereotypy responses to amphetamine. *Nature* **230:** 30-32, 1971.
38. Sulser, F., J. Vetulani and P. L. Mobley. Mode of action of antidepressant drugs. *Biochem Pharmacol* **27:** 257-261, 1978.
39. Thaxton, L. Physiological and psychological effects of short-term exercise addiction on habitual runners. *J Sport Psychol* **4:** 73-80, 1982.
40. Thornburg, J. E. and K. E. Moore. The relative importance of dopaminergic and noradrenergic neuronal systems for the stimulation of locomotor activity induced by amphetamine and other drugs. *Neuropharmacology* **12:** 853-866, 1973.
41. U'Prichard, D. L., D. A. Greenberg, P. P. Sheehan and S. Snyder. Tricyclic antidepressants: therapeutic properties and affinity for β adrenergic receptor binding sites in the brain. *Science* **199:** 197-198, 1978.
42. U'Prichard, D. C. and R. Kvetnansky. Central and peripheral adrenergic receptors in acute and repeated immobilization stress. In: *Catecholamines and Stress: Recent Advances*, edited by E. Usdin, R. Kvetnansky and I. J. Kopin. New York: Elsevier/North Holland, 1979, pp. 279-308.
43. Waldmeier, P. C., P. A. Baumann and L. Maitre. CGP 6085 A, a new specific, inhibitor of serotonin uptake: neurochemical characterization and comparison with other serotonin uptake blockers. *J Pharmacol Exp Ther* **211:** 42-49, 1979.
44. Weiss, J. M., W. H. Bailey, L. A. Pohorecky, D. Korgeniowski and G. Grillione. Stress-induced depression of motor activity correlates with regional changes in brain norepinephrine but not in dopamine. *Neurochem Res* **5:** 9-22, 1980.
45. Weiss, J. M., H. I. Glazer, L. A. Pohorecky, J. Brick and N. E. Miller. Effects of chronic exposure to stressors in avoidance-escape behavior and of brain norepinephrine. *Psychosom Med* **37:** 522-534, 1975.
46. Wolfe, B. B., T. K. Harden, J. R. Sporn and P. B. Molinoff. Presynaptic modulation of beta adrenergic receptors in rat cerebral cortex after treatment with antidepressants. *J Pharmacol Exp Ther* **107:** 446-457, 1978.
47. Yamamoto, B. K. and C. R. Freed. The trained circling rat: a model for inducing unilateral caudate dopamine metabolism. *Nature* **298:** 467-468, 1982.
48. Zivin, J. A. and D. R. Waud. How to analyze binding, enzyme and uptake data: The simplest case, a single phase. *Life Sci* **30:** 1407-1422, 1982.