Influence of Training and Pharmacological Treatment on Muscular Enzymatic Activities

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Abstract □ The adaptation of some enzymatic activities of glycogenolysis (adenyl cyclase and phosphorylase), glycolysis (phosphofructokinase, pyruvate kinase, and lactate dehydrogenase), the tricarboxylic acid cycle (citrate synthase, isocitrate dehydrogenase, 2-ketoglutarate dehydrogenase, and malate dehydrogenase), and subsidiary pathways of pyruvate metabolism (glutamate pyruvate transaminase) was studied in the rat as a function of training time (25, 50, 100, 125, and 150 days). The workload was set at 25 m/min for 150 min/day. Some groups of animals were treated daily with vasodilators such as papaverine, caffeine, nicergoline, or bamethan. With a steady daily workload, at least three different periods can be recognized as a function of training time: (*a*) noncompensated mitochondrial adaptation, where an increase is observed both in the Krebs cycle enzymatic activities and in the enzymatic activities related to glycogenolysis and glycolysis; (*b*) compensated mitochondrial adaptation, where mitochondrial enzymatic activities further increase while activities of glycogenolysis and glycolysis return to base values; and (*c*) overcompensated mitochondrial adaptation, where mitochondrial enzymatic activities are in a steady state while pyruvate is largely transaminated to 2-ketoglutarate and somewhat reduced to lactate. The phase of mitochondrial adaptation is compensated for by the actual workload performed. As a consequence, a variation in the intensity factor causes the biological system to go back to the stage of mitochondrial noncompensation. Drugs play a role during the phase of noncompensated mitochondrial adaptation by modifying the aerobic mechanism (*e.g.*, nicergoline), the anaerobic mechanism (*e.g.*, caffeine), or both (*e.g.*, bamethan). These actions do not seem to be ascribable to the vasodilating properties of these drugs, since papaverine is always inactive. The administration of the drugs is totally ineffective when the adaptation of enzymatic activities to the endurance workload has been reached.

Keyphrases □ Enzyme activity—effect of training time and treatment with various vasodilators, rats □ Vasodilators—papaverine, caffeine, nicergoline, and bamethan, effect on muscular enzyme activity, rats □ Training time—effect on muscular enzyme activity, rats □ Papaverine—effect on muscular enzyme activity, rats □ Caffeine—effect on muscular enzyme activity, rats □ Nicergoline—effect on muscular enzyme activity, rats □ Bamethan—effect on muscular enzyme activity, rats

Blood and muscular concentrations of lactate and pyruvate during a submaximal exercise are lower in trained subjects than in untrained ones (1–4), the pyruvate being metabolized through the potentiation of various metabolic pathways as a function of training. Indeed, adequate endurance training causes an increase in mitochondrial oxidative power (5–7). Therefore, one might assume that the increased oxidation of pyruvate represents a decisive limiting factor, at least at the mitochondrial level.

In the Krebs cycle, the metabolic fate of acetyl coenzyme A is closely related to the condensation reaction with oxaloacetate. Consequently, the availability of oxaloacetate in the muscle becomes a limiting factor, both because of the condensation reaction and because of the catalytic reaction caused by the oxaloacetate dependence of the citrate synthase. In this case, the shunt of pyruvate to 2-ketoglutarate, malate, or oxaloacetate might represent an important subsidiary metabolic pathway (8–10).

Pharmacological treatment may influence enzymatic adaptation to endurance training, but virtually no data are available except for results showing that some vasodilating drugs can anticipate the time increase of some mitochondrial enzymatic activities induced in muscle by training. However, these drugs do not modify the plateau of these enzymatic activities, nor do they contribute to maintaining the level attained against the spontaneous decrease as a response to reduced muscular work (5).

In this investigation, the effect of training on the activity of the enzymes of glycogenolysis, glycolysis, the tricarboxylic acid cycle, and possible subsidiary pathways of pyruvate metabolism in the gastrocnemius muscle of rats was studied. In addition, the effect of some vasodilating drugs (papaverine, caffeine, nicergoline, and bamethan) on enzymatic adaptation was evaluated.

EXPERIMENTAL

Male Wistar rats (n = 151), 120–140 g, were chosen from a group of 400 animals raised under standard conditions (temperature, 23 ± 1°; and relative humidity, 55–60%) and fed a pellet diet[1] and water *ad libitum*.

During the first stage, 400 rats were submitted to psychomotor adaptation for 6 days/week for 2 consecutive weeks on a rotarod apparatus[2] in which the performance time could be recorded automatically. During this stage, the animals increased their motor activity from 2.5 to 10 m/min. For the second stage, 200 rats were chosen whose average performance time at the rate of 10 m/min, after the training period, was close to the mean of the sample examined.

In the exercising animals, the continuous run was progressively increased from 20 m/min for 60 min/day to 25 m/min for 150 min/day within a maximum of 50 days. The animals that were not able to attain this working capacity within this time were discarded. Consequently, the enzymatic recordings on the 25th day were carried out on the assumption that the animals examined would execute their performance within the established time. At any rate, the recordings on the 25th day were carried out in rats with a working capacity of 25 m/min for at least 120 min/day. Progressing from this workload to that of the 50th day (25 m/min for 150 min/day) caused the discarding of approximately 20% of the animals.

In addition to the training activity, 103 animals were treated daily with 0.5 ml/kg ip of a 1.6, 4, or 10×10^{-3} M solution of papaverine, caffeine, nicergoline, or bamethan. The rats were submitted to the test 30 min after treatment. For these drugs, these dosages fall in the range commonly used experimentally.

The 151 rats finally examined were taken from the following lots: (*a*) sedentary rats (n = 8); (*b*) rats trained for 25 days (n = 8); (*c*) rats trained for 25 days and treated with the three dose levels (0.5 ml/kg ip of 1.6, 4, or 10×10^{-3} M solutions) of one of the four drugs (n = 63); (*d*) rats trained for 50 days (n = 8); (*e*) rats trained for 100 days (n = 8); (*f*) rats trained for 100 days and treated with 0.5 ml/kg ip of a 4×10^{-3} M solution of one of the drugs tested (n = 20); (*g*) rats trained for 125 days (n = 8); (*h*) rats trained for 150 days (n = 8); and (*i*) rats trained for 150 days and treated with 0.5 ml/kg ip of a 4×10^{-3} M solution of one of the drugs tested (n = 20).

The biochemical observations were carried out after 25, 50, 100, 125, and 150 days of training. Training was discontinued 72 hr prior to sacrifice. The rats were then beheaded, and their gastrocnemius muscles were isolated from the surrounding tissue and rapidly weighed. The muscle homogenates were prepared according to standard procedures (11) using 250 mM sucrose as the homogenization medium. The operative procedure was performed in a precooled refrigerator with a Potter–Elvehjem apparatus at 0–5°. The homogenates were diluted to 10% (w/v) before

[1] Rieper.
[2] Basile Research Instruments, Comerio, Italy.

Table I—Activities of Gastrocnemius Muscle Enzymes of Sedentary Rats and of Rats Trained to Run Continuously for 150 min/day at 25 m/min [a]

Exercise Group	Adenyl Cyclase $\times 10^{-6}$	Phospho-rylase	Phospho-fructo-kinase	Pyruvate Kinase	Lactate Dehydro-genase	Citrate Synthase	Isocitrate Dehydro-genase	2-Keto-glutarate Dehydro-genase	Succinate Dehydro-genase	Malate Dehydro-genase	Glutamate Pyruvate Trans-aminase
Seden-tary	28.6 ± 1.7	19.6 ± 1.3	31.2 ± 2.5	248 ± 12	516 ± 11	22.7 ± 1.9	2.65 ± 0.16	1.24 ± 0.11	3.84 ± 0.19	278 ± 27	21.4 ± 1.2
25 Days	52.4[b] ± 3.9	29.6[b] ± 1.1	45.6[b] ± 3.4	338[b] ± 23	759[b] ± 74	32.5[b] ± 1.8	3.92[b] ± 0.29	1.66 ± 0.10	5.33[b] ± 0.29	366 ± 26	20.3 ± 1.5
50 Days	32.5 ± 2.1	21.2 ± 1.7	35.3 ± 2.5	287 ± 8	592 ± 21	36.6[b] ± 1.7	4.45[b] ± 0.23	1.74 ± 0.10	6.33[b] ± 0.26	411[b] ± 42	24.3 ± 2.3
100 Days	26.5 ± 1.7	18.6 ± 1.1	26.8 ± 2.6	204 ± 20	485 ± 17	41.6[b] ± 3.2	5.12[b] ± 0.34	1.92[b] ± 0.09	6.97[b] ± 0.27	444[b] ± 38	33.3[b] ± 1.4
150 Days	30.6 ± 1.5	22.2 ± 0.6	33.8 ± 1.2	271 ± 9	366[b] ± 29	44.5[b] ± 1.8	5.16[b] ± 0.22	1.85[b] ± 0.11	7.17[b] ± 0.32	464[b] ± 14	51.3[b] ± 3.1

[a] The activities are expressed as micromoles of substrate utilized per minute per gram wet weight of tissue. Values are means ± *SEM* of eight rats. [b] Significantly different from controls, $p < 0.01$ (Student t test).

fractionation and then centrifuged[3] at 700×*g* for 10 min.

The supernate was decanted and centrifuged again at 700×*g* for 10 min. The supernate was then centrifuged at 14,000×*g* for 15 min, and the pellet was suspended in 250 m*M* sucrose (11). The following enzymatic activities were evaluated: adenyl cyclase (12, 13), phosphorylase (14), phosphofructokinase (15), pyruvate kinase (15), lactate dehydrogenase (16), citrate synthase (17, 18), isocitrate dehydrogenase (19), 2-ketoglutarate dehydrogenase (20), succinate dehydrogenase (21), malate dehydrogenase (15, 22), and glutamate pyruvate transaminase (10). Protein concentration was determined according to Lowry *et al.* (23).

Spectrophotometric assays were performed in a double-beam spectrophotometer[4] with a thermostated cell compartment, in 3-ml cells of 1-cm light path, at 25°. Initial reaction rates were determined from a segment of the linear portion of the change in absorbance and corrected for the rates of any nonspecific activity. The assays were performed only under conditions where the reaction rate was proportional to enzyme concentration. The enzymatic activities are referred to as micromoles of substrate utilized per minute per gram of fresh tissue.

RESULTS

In the rat gastrocnemius muscle, the enzymatic adaptation to intensive endurance training (25 m/min for 150 min/day) occurred in both the hyaloplasm and the mitochondria. On the 25th day of training, several mitochondrial enzymatic activities were significantly increased (citrate synthase, isocitrate dehydrogenase, and succinate dehydrogenase), while others were not significantly modified (2-ketoglutarate dehydrogenase and malate dehydrogenase) (Table I). At the same time, a significant increase in the enzymatic activities of both glycogenolysis (adenyl cyclase and phosphorylase) and glycolysis (phosphofructokinase, pyruvate kinase, and lactate dehydrogenase) was observed.

The findings relative to the 50th and 100th days of training demonstrated a progressive increase in mitochondrial enzymatic activities, whereas by that time hyaloplasmic activities had returned to base values (Table I). This result proves that mitochondrial activity tended to reach steady state with the endurance muscular work to which the animals were submitted.

Following this steady-state phase, while training was regularly being carried on at the rate and intensity described, a marked increase in the activity of glutamate pyruvate transaminase and a decrease in the lactate dehydrogenase activity were found on the 150th day of training (Table I). This finding indicates that the former enzyme was increasingly capable of competing for pyruvate with the latter one, thus making pyruvate exceeding the Krebs cycle available more for transamination to 2-ketoglutarate than for reduction to lactate.

All these enzymatic adaptations were directly related with the endurance workload. Table II shows the results obtained in animals trained for 100 days at 25 m/min for 150 min/day and then submitted to a workload of 30 m/min for 150 min/day during the following 25 days. In these animals, which were already in a steady state between endurance work intensity and mitochondrial enzymatic adaptation, the daily work intensity was only moderately increased. Nevertheless, the rate change (from 25 to 30 m/min) was more than sufficient to modify the steady state and to increase significantly both glycogenolysis and glycolysis enzymatic activities. Therefore, this situation was analogous to the initial one observed when sedentary rats were submitted to the endurance work.

In some animals, the training (25 m/min for 150 min/day) was associated with the intraperitoneal administration of three doses of drugs exerting a peripheral vasodilating action. On the 25th day of training, papaverine was not inducing any significant change in the enzymatic activities examined (Table III). Caffeine caused an increase in several glycogenolysis and glycolysis activities but no significant modifications in mitochondrial enzymatic activities. With nicergoline, succinate dehydrogenase and malate dehydrogenase activities were increased, while lactate dehydrogenase was significantly decreased. Finally, the admin-

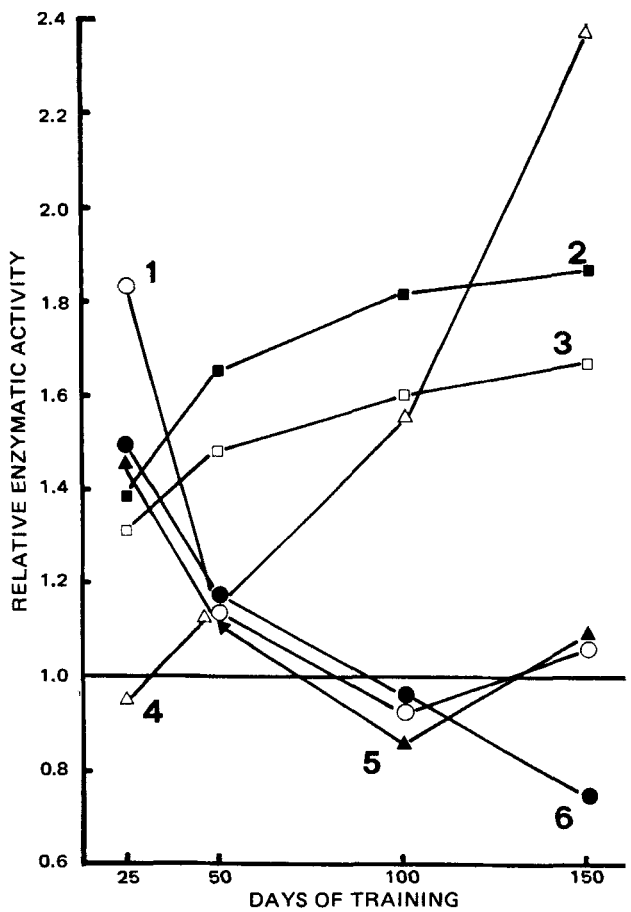

Figure 1—*Relative enzymatic activities of gastrocnemius muscle of rats trained to run continuously for 150 min/day at 25 m/min, expressed as a function of training time. Enzymatic activity was expressed by assuming the activity of sedentary controls (at time 0) was equal to 1. Each point represents the mean of eight rats. Key: 1, adenyl cyclase; 2, succinate dehydrogenase; 3, malate dehydrogenase; 4, glutamate pyruvate transaminase; 5, phosphofructokinase; and 6, lactate dehydrogenase.*

[3] Sorvall RC-5 supercentrifuge.
[4] Perkin-Elmer 124/56.

Table II—Activities of Gastrocnemius Muscle Enzymes of Rats Trained to Run Continuously for 150 min/day for 100 Days at 25 m/min with or without Subsequent Training for 25 Days at 30 m/min [a]

Exercise Group	Adenyl Cyclase $\times 10^{-6}$	Phospho-rylase	Phospho-fructo-kinase	Pyruvate Kinase	Lactate Dehydro-genase	Citrate Synthase	Isocitrate Dehydro-genase	2-Keto-glutarate Dehydro-genase	Succinate Dehydro-genase	Malate Dehydro-genase	Glutamate Pyruvate Trans-aminase
100 Days at 25 m/min	26.5 ± 1.7	18.6 ± 1.1	26.8 ± 2.6	204 ± 20	485 ± 17	41.6 ± 3.2	5.12 ± 0.34	1.92 ± 0.09	6.97 ± 0.27	444 ± 38	33.3 ± 1.4
100 Days at 25 m/min + 25 days at 30 m/min	44.7[b] ± 4.0	26.8[b] ± 2.0	38.8[b] ± 1.6	285 ± 14	687[b] ± 34	43.2 ± 2.6	5.26 ± 0.18	2.15 ± 0.13	7.23 ± 0.23	470 ± 36	40.3 ± 3.4

[a] The activities are expressed as micromoles of substrate utilized per minute per gram wet weight of tissue. Values are means ± *SEM* of eight rats. [b] Significant difference, $p < 0.01$ (Student t test).

istration of bamethan significantly increased both adenyl cyclase and succinate dehydrogenase activities.

However, these pharmacological actions were no longer observable in animals trained and treated for 100 or 150 days (Table IV). This finding suggests that drugs act only during the first stage of noncompensated physiological adaptation to endurance training. Indeed, after physiological adaptation had taken place, the drugs tested were totally inactive.

DISCUSSION

For the same endurance workload, the evaluated muscular enzymatic activities varied in a nonhomogeneous way as a function of the training time. Changes in the hyaloplasmic enzymatic activities were different from those observed in the mitochondrial ones. Among mitochondrial activities themselves, those of the tricarboxylic acid cycle showed quantitatively different modifications. However, these discrepancies in behavior can be partially regarded as merely apparent ones. With an effective workload (5), at least three successive phases (as a function of the training time) can be hypothesized.

Noncompensated Mitochondrial Adaptation—The initial increase (Fig. 1) in the mitochondrial enzymatic activities of the Krebs cycle was accompanied by a significant increase in the hyaloplasmic ones. In particular, the increased activity of adenyl cyclase and phosphorylase and of phosphofructokinase and pyruvate kinase demonstrates the activation of glycogenolysis and glycolysis, respectively. The increase in the lactate dehydrogenase activity suggests that a certain amount of pyruvate is reduced to lactate instead of being utilized as acetyl coenzyme A in the tricarboxylic acid cycle. If this were the case, the adaptation of mitochondrial activities would not be able to meet the actual energy requirements consequent to training and the lactacid anaerobic compensative mechanism would then activate.

This hypothesis is further supported by the role of the drugs tested. Nicergoline is an α-blocking agent that activates the mitochondrial oxidative processes (5, 24–26) and, in part, the adenyl cyclase system (27). As compared to trained untreated animals, during this first stage nicergoline (Fig. 2) caused both an increase of several mitochondrial enzymatic activities and a lower training-induced increase in the lactate dehydrogenase activity.

Caffeine is a xanthine drug, known to activate the adenyl cyclase system through phosphodiesterase inhibition (28). As compared to trained untreated animals, during this first stage caffeine did not significantly increase mitochondrial activities, but it increased the activity of adenyl cyclase (activation of glycogenolysis), phosphofructokinase (activation of glycolysis), and lactate dehydrogenase (activation of the reduction of pyruvate to lactate). Bamethan is a catecholamine-like agent, stimulating the adenyl cyclase system (29) and partially the oxidative processes (24, 25). As compared to trained untreated animals, bamethan induced an increase in a few mitochondrial activities and in the hyaloplasmic enzymatic activity adenyl cyclase.

The behavior of enzymatic systems, examined also with regard to the effect of varying exogenous stimuli (such as those caused by the drugs tested), confirmed the existence of a "see-saw" mechanism between mitochondrial oxidative adaptation and the lactacid anaerobic mechanism to meet the energy requirements consequent to training.

Finally, it should be stressed that chronic administration of papaverine at the doses capable of exerting an effective peripheral vasodilating action did not change any glycolytic and mitochondrial enzymatic activities.

Compensated Mitochondrial Adaptation—With training continuing at the set constant level, the progressive increase in the Krebs cycle mitochondrial enzymatic activities became more evident during the second phase. However, the enzymatic activities connected with glycogenolysis and glycolysis showed a constant decrease, down to values close to the initial pretraining ones (Fig. 1). During this phase, the increase in mitochondrial activities would appear to be able to meet the energy requirements brought about by training, with no need for any hyaloplasmic compensation. During this phase, the chronic treatment with the drugs tested did not modify the overall pattern of mitochondrial adaptation phenomena.

Overcompensated Mitochondrial Adaptation—With training continuing at the set intensity level, mitochondrial enzymatic activities were practically in a steady state. However, a concomitant increase was noted in some enzymatic activities connected with pyruvate metabolic pathways (*e.g.*, pyruvate + glutamate $\rightleftharpoons$ alanine + 2-ketoglutarate, catalyzed by glutamate pyruvate transaminase) (Fig. 1). Lactate dehydrogenase was, on the other hand, decreased to values lower than pretraining ones. Therefore, during this phase, even though mitochondrial enzymatic activities were adequate to the daily workload, a "third way"

Table III—Activities of Gastrocnemius Muscle Enzymes of Rats Trained to Run Continuously for 150 min/day at 25 m/min for 25 Days with or without Drug Treatment (0.5 ml/kg ip Daily of a 1.6, 4, or 10 $\times 10^{-3}$ *M* Solution) [a]

Trained Group	Concen-tration, $M \times 10^{-3}$	n	Adenyl Cyclase $\times 10^{-6}$	Phospho-rylase	Phospho-fructo-kinase	Lactate Dehydro-genase	Citrate Synthase	Succinate Dehydro-genase	Malate Dehydro-genase	Glutamate Pyruvate Trans-aminase
Untreated	—	8	52.4 ± 3.9	29.6 ± 1.1	45.6 ± 3.4	759 ± 74	32.5 ± 1.8	5.33 ± 0.29	366 ± 26	20.3 ± 1.5
Treated with caffeine	1.6	5	66.3[b] ± 3.7	35.2 ± 3.9	52.4 ± 4.4	850 ± 21	29.2 ± 1.7	5.04 ± 0.36	321 ± 17	24.6 ± 2.7
	4.0	5	68.9[b] ± 5.4	34.8 ± 3.0	56.3[b] ± 2.3	905[b] ± 23	35.2 ± 1.4	5.40 ± 0.46	375 ± 10	21.6 ± 1.5
	10.0	5	70.2[b] ± 4.6	33.3 ± 2.8	58.4[b] ± 3.1	876[b] ± 32	31.4 ± 2.3	4.92 ± 0.61	354 ± 16	17.6 ± 3.8
Treated with papaverine	1.6	5	52.6 ± 3.3	25.6 ± 3.1	40.6 ± 2.6	730 ± 64	27.7 ± 3.6	5.52 ± 0.46	348 ± 21	19.9 ± 2.2
	4.0	5	49.2 ± 4.1	26.6 ± 2.4	47.1 ± 2.6	782 ± 35	30.2 ± 2.2	5.20 ± 0.21	324 ± 23	22.1 ± 1.6
	10.0	5	47.7 ± 3.2	24.7 ± 2.5	39.2 ± 1.8	765 ± 71	29.3 ± 1.8	5.28 ± 0.17	402 ± 61	24.3 ± 1.9
Treated with bamethan	1.6	5	60.2 ± 4.8	29.9 ± 2.1	43.6 ± 2.2	858 ± 70	32.4 ± 2.7	5.96 ± 0.31	336 ± 26	19.1 ± 2.0
	4.0	5	69.5[b] ± 5.0	33.5 ± 3.3	52.6 ± 3.1	842 ± 53	37.3 ± 1.7	6.37[b] ± 0.19	404 ± 28	23.0 ± 1.6
	10.0	5	71.8[b] ± 6.3	37.4[b] ± 1.7	47.4 ± 3.6	836 ± 50	37.6 ± 2.0	6.23[b] ± 0.24	473[b] ± 28	25.6 ± 3.7
Treated with nicergoline	1.6	6	49.4 ± 4.6	27.2 ± 1.3	39.4 ± 4.2	613[b] ± 48	36.6 ± 2.9	6.18[b] ± 0.37	394 ± 17	20.6 ± 1.9
	4.0	6	57.6 ± 1.9	31.2 ± 1.5	47.7 ± 1.8	642[b] ± 14	40.4 ± 3.5	6.74[b] ± 0.41	438[b] ± 25	22.5 ± 1.8
	10.0	6	58.4 ± 2.6	29.2 ± 1.4	41.3 ± 3.3	600[b] ± 36	40.2 ± 4.1	6.82[b] ± 0.51	444[b] ± 36	21.4 ± 1.7

[a] The activities are expressed as micromoles of substrate utilized per minute per gram wet weight of tissue. Values are means ± *SEM* of n rats. [b] Significantly different from trained untreated rats, $p < 0.01$ (Student t test).

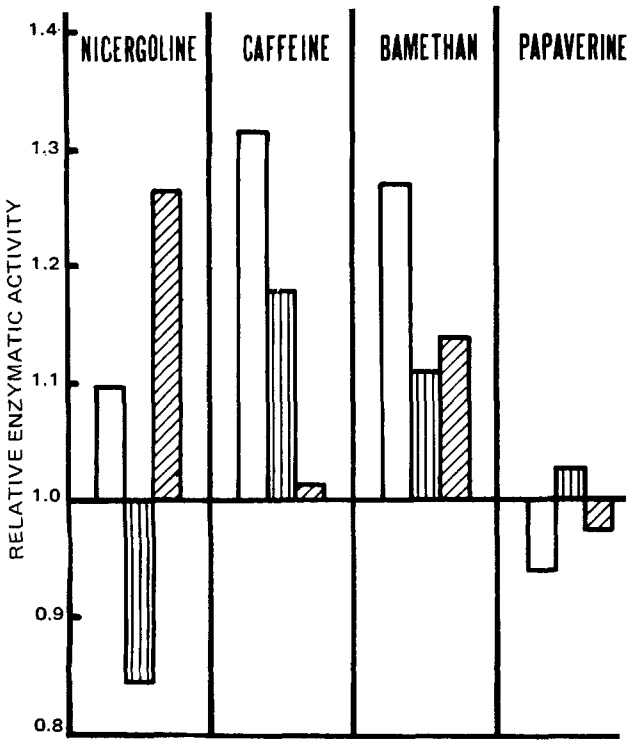

Figure 2—*Relative enzymatic activities of gastrocnemius muscle of rats trained to run continuously for 150 min/day at 25 m/min for 25 days and treated daily with drugs (0.5 ml/kg ip of a 4 × 10^{-3} M solution) expressed as a function of the activity of trained untreated rats. Key:* □, *adenyl cyclase;* ▩, *lactate dehydrogenase; and* ▨, *succinate dehydrogenase.*

of pyruvate metabolism became evident. This side pathway (8, 10) would permit the utilization of pyruvate instead of its reduction to lactate.

Under those experimental conditions (*i.e.*, constant intensity and duration of work), this further specialization of a metabolic shunt with the Krebs cycle, at a time when the values of the enzymatic activities of the Krebs cycle itself have reached a high plateau, seems rather strange. Moreover, it is not totally clear why, for example, after 100 days of training some enzymatic activities of the Krebs cycle had increased by 80–90% (*e.g.*, isocitrate dehydrogenase and succinate dehydrogenase) while others had increased by only 50–60% (*e.g.*, 2-ketoglutarate dehydrogenase and malate dehydrogenase).

The methods used to determine enzymatic activities completely upset the autoregulative interactions that maintain the cell as a functionally integrated system (5). A thorough and reliable picture of enzymatic functions can be provided only by an extensive investigation of biochemical relationships at the subcellular level. Indeed, an evaluation of the activity of an enzyme cannot yield any information about the concentration of the enzyme itself. Nor can an overall evaluation of mitochondrial proteins give reliable information on the concentration of a single mitochondrial enzyme. Nevertheless, even knowing the amount of the purified enzyme provides little satisfactory information when the characteristic more effectively modulated by training or by drug is, for example, the affinity between the enzyme and the substrate. Absolute conclusions are not drawn from experimental data which, even though numerous and sophisticated, might be only relatively related to each other.

The phases of mitochondrial adaptation are relative to the actual workload. Thus, after the phase of compensated mitochondrial adaptation, an increase in the workload causes biological substrates to go back to the state of noncompensated mitochondrial adaptation. Significant increases in the enzymes of glycogenolysis (adenyl cyclase and phosphorylase), glycolysis (phosphofructokinase), and pyruvate reduction (lactate dehydrogenase) are again induced.

Only the phase of noncompensated mitochondrial adaptation seems to be affected by drugs, with the extent depending more on the drug's specific characteristics than on its vasodilating action. Some drugs act mainly on oxidative processes (nicergoline), others act on glycolysis

Table IV—Activities of Gastrocnemius Muscle Enzymes of Rats Trained to Run Continuously for 150 min/day at 25 m/min for 100 Days with or without Treatment by Some Drugs (0.5 ml/kg ip Daily of a 4 × 10^{-3} *M* Solution)

Trained Group	*n*	Adenyl Cyclase × 10^{-6}	Lactate Dehydrogenase	Succinate Dehydrogenase
Untreated	8	26.5 ± 1.7	485 ± 17	6.97 ± 0.27
Treated with caffeine	5	30.2 ± 2.6	510 ± 22	7.10 ± 0.37
Treated with papaverine	5	24.3 ± 2.4	510 ± 25	6.65 ± 0.20
Treated with bamethan	5	31.2 ± 3.6	503 ± 33	6.72 ± 0.27
Treated with nicergoline	5	27.6 ± 1.8	468 ± 24	7.20 ± 0.35

[a] The activities are expressed as micromoles of substrate utilized per minute per gram wet weight of tissue. Values are means ± *SEM* of *n* rats.

(caffeine), while still others exhibit intermediate characteristics (bamethan). With regard to the phases of compensated mitochondrial adaptation, the drugs tested proved totally inactive.

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