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THE MITIGATION OF PHYSICAL FATIGUE WITH "SPARTASE"

FRANCIS J. NAGLE, Ed.D. BRUNO BALKE, M.D. RICHARD V. GANSLEN, Ph.D. AUDIE W. DAVIS, JR., M.D.

Biodynamics Branch

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THE MITIGATION OF PHYSICAL FATIGUE WITH "SPARTASE"

Francis J. Nagle, Ed.D. Bruno Balke, M.D. Richard V. Ganslen, Ph.D. Audie W. Davis Jr., M.D.

ABSTRACT

Pharmacological and clinical observations have indicated that Spartase – the aspartic acid salts of potassium and magnesium – takes part in the intermediary metabolism and moderates physical fatigue. In this study attempts were made to evaluate effects of the drug on work capacity before and after episodes of physically fatiguing exercises. Work capacity was determined by a standardized treatmull text. The text was repeated after the subject had been running cross-country for a period of 60 minutes, and again after another such period of 40 minutes. In this way effects of fatigue upon functional adaptability to stress became apparent. Then, Spartase was taken orally in a prescribed dose for two weeks whereupon the same testing procedure was reapplied. The results indicated that Spartase improved the endurance performance of untrained individuals engaging in estremaly fatiguing physical work. It appeared to have no effect on highly trained individuals.

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Fatigue is a normal consequence of mental and physical work and apparently an essential factor in the establishment of the rhythmic cycle of wakefulness and sleep. It is accompanied by biological properties adverse to good performance capacity. Although these properties are reversible under conditions of adequate cest, man has long sought for physical or chemical means to prevent or moderate fatigue induced disturbances in the organism, thus extending periods of work at peak efficiency.

One of the drugs reputed to moderate physical fatigue is Spartase⁶ — the trade name for the potassium and magnesium salts of aspartie neid. Aspartie acid is a non-essential glycogenie amino acid, playing some role in protein metabolism where urea is the end product. It is, according to Ratner,¹⁰ the specific nitrogen denor in the conversion of citrulline to arginine which occurs anaerobically in the presence of magnesium ions and adenosine triphosphate in the omithine cycle, Of possible significance is the fact that the ornithing cycle is related to the energy producing Krebs cycle as schematically shown in Figure 1.

Clinical and laboratory investigations have indicated that potassium and magnesium aspartates can moderate physical fatigue. Kruse" and Vial" have reported reductions in the subjective symptoms of fatigue, the former treating patients with Spartase, the latter administering it to trained athletes.

Extensive work has been reported in which the electronic rheotome was used as a tool for performance evaluation. The rheotome permits muscle excitation by electric stimulation of the proper motor nerves in designated cutaneous areas, or by stimulation of underlying muscles directly. The relationship of intensityduration curves for nerve and muscle, which, according to the investigators is characteristic of the fatigue state, has been shown to revert back to normal following treatment with Spartase.^{10,144}

The purpose of this investigation was to study objectively the effect of the drug on work capacity by measuring the physiological

[&]quot;Interview and magnetium aspectates used in this study were provided by Wheth Laboratories as Spartase.

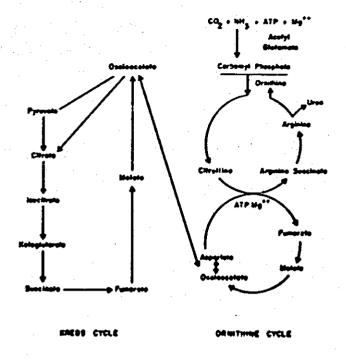


Figure 1. - This schematic illustrates the involvement of Aspartate in the Ornithine Cycle and the linking of the Ornithine Cycle with the Krebe Cycle.

adjustments to increasingly demanding physical work under normal conditions and in various states of fatigue.

PROCEDURE

The experimental plan called for the evaluation of work capacity under normal conditions and at two different stages of induced physical fatigue. This was accomplished by determining the biodynamic potential of four subjects on a treadmill by means of a Work Capacity Test (WCT) described elsewhere.¹⁰ The subjects were thoroughly rested and in a postabsorptive state.

Immediately following .he first test (WCT I) the subjects ran for 60-minutes on a country road, attempting to cover the greatest possible distance during that time period. This activity caused a certain amount of physical fatigue which was made evident in WCT II administered immediately after returning from the 60minute run. After another best-effort run of 40 minutes duration the fatiguing consequences of the overall effort were evaluated in a final WCT III.

Four normal subjects of 21, 32, 38 and 55 years of age participated in the study. Subject A (21) was a college student trained for competitive cross-country running. Subject B (38) followed a regular training regimen, running from one to four miles three times each week. Subject C (32) played occasional tennis but had not participated in physical exercises of any significance for four weeks prior to the experimients. Subject D (55), out of regular training for several months, ran distances of 2-3 miles once or twice a week.

For Subject C the two periods of roadrunning were replaced by equivalent but more readily controllable work-out; in the treadmill. During the treadmill tests pulse rate, blood pressure and pulmonary ventilation were measured at regular intervals and the oxygen intake and carbon dioxide output were determined at the crest load. The total energy expenditures during the running periods were estimated from the oxygen requirements for given running velocities.⁶⁶⁷ In the treadmill experiments, the speed and slope of the belt served as factors for the estimation of oxygen intake and total energy out-put.⁶⁷⁷

Considering the possibility of changes in orthostatic tolerance due to physical fatigue, tilt table tests were carried out on each subject before the first and following the last WCT of each experimental series. During 5 minutes in the supine position, for 7 minutes tilted footward to 60 degrees and for 3 minutes following the return to the horizontal, pulse rate and blood pressure were measured in half-minute intervals. In addition, one-lead ECG tracings from chest electrodes were obtained during the tilt and exercise experiments.

After the "control" responses to this complete test procedure had been established, the Spartase regimen was begun. Four tablets of 250 mg potassium aspartate and 250 mg magnesium aspartate each were taken daily for a period of one week by Subject D and for two weeks by the other three subjects. Then, the entire testing procedure was repeated in a second series, under external environmental conditions nearly identical to those of the first series as shown in Table 1.

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RESULTS

The course of the entire exercise procedure and the functional adjustments observed during its various phases are shown by the data of Subject B in Figure 2. The subject's cardiorespiratory responses to the gradually increasing energy demands, the latter expressed in amounts of oxygen required per unit of body weight, provide a proper accounting of his functional reserves and limitations during each of the Work Capacity Tests. In this particular case, the subject attained a maximum oxygen intake of 44.2 m1/kg/min in the first "control" test and then worked at an estimated 88 per cent of this potential capacity during the 60-minute run. The physical fatigue resulting from this effort caused a considerable reduction of work capacity in WCT II. Accordingly, the average performance during the second steady state period of work, running 40 minutes, was lower than during the first period. The maximum oxygen intake at the end of the third WCT was only 72 per cent of that attained in WCT I. Although, for any given workload, the pulmonary ventilation increased with accumulating fatigue, the peak volume at the end

TABLE 1

SUBJECT	CONTROL TEMP "C	EXPERIMENTS HUMIDITY %	SMATASE TEMP. "C	EXPERIMENTS HUMOITY 15
· ▲	30	83	38	49
B ., .	32.	e., "44	31	61

EMPERATURE AND R. ATIVE HUNDITY DURING THE OUT-DOOR RUNS !

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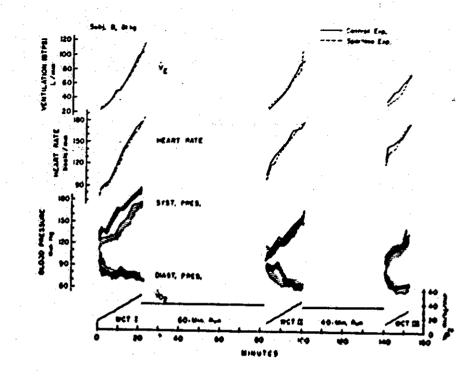


Figure 2. - Physiological data secured during work capacity tests in Control and Spartase series of experiments on well trained subject.

of each successive test was lower than in the previous test. For this experimental subject the values were 104, 94, and 76 1/min (BTPS) for WCT I, II and III, respectively.

Figure 2 also shows the test results after the administration of Spajitase. The subject's functional response pattern as well as the performance capacity in all three tests were nearly identical, However, in case of Subject D (Figure 3) Spartase appeared to have altered the pattern of cardiorespiratory adjustments in response to the same energy demands. Hemodynamic conditions were apparently more economical (lower pulse rate and pulse pressure) and the ventilatory efficiency was certainly improved in WCT II and III (less volume of air moved at same oxygen requirement). The subject was not only able to perform more work during the 40-minute run, but also demonstrated a considerable improvement of work capacity in the last test,

The essential performance data of all four subjects are shown in Table 2. Because body weights changed considerably during the experimental procedure, the minute values for

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maximum oxygen intake (in the work espacity tests) and for the average oxygen requirements during the running periods were presented in milliliters per kilogram of hody weight. Since maximum oxygen intake served as the main performance criterion, the various work levels attained were expressed in per cent of the oxygen intake achieved in the first "control" test.

Considering the decline of performance from WCT I to WCT III as most significant for the assessment of "physical fatigue," the results obtained in the "control" tests revealed for all four subjects, a decrease to 64-72 per cent of the original work capacity as a consequence of the preceding rhysical efforts. In the Spartase experiments the two well-trained individuals experienced essentially the same performance deterioration as in the "control" experiments. The two physically less active subjects, however, demonstrated an increase of functional and metabolic reserves in the final test, their tim. from oxygen intake being 33.3 for Subject C and 36.5 m1/kg for Subject D compared to _6.8 and 27.9 m1/kg, respectively, in "control"

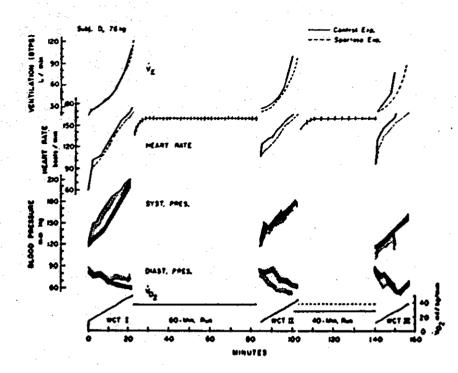


Figure J. - Physiological data secured during work capacity tests in Control and Spartase series of experiments on untrained subject.

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		•	al/b	j∕nin	•	•	•	•	ei/b	Vinin		•
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	· .		546.A	67 7	•				PHILE.	17 7	•	
ýct z	64.6	64.3	97,8	14.2	100		01,7	80.3	44,8	48.1	100	100
BO-min, run	••	••	18.8					•••	37.9	38.0		
WCT I	4.5	42,4	48.6	44.8			71.5	78.0	40.9	38.0	98	
40-min, run			38.5	36.7	•7	4	•••		38,4	38.4	-	
WCT III	4 2	60.6	37.0	38,4		0	ne	78.0	31.7	84.0	72	
ť	1						<u> </u>					
· · ·	•		MAR	17 °C	•					r 7	•	
WCT I	71.7	71.3	40.0	44.7	100	Im	78.2					10

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WCT I	71,7	71,3	40.0	44.7	100	111	18.2	77,1	43,5	44.6	100	108
80-min, run		4.	30.6	30.6	'76	10	**	+4	34.5	36.5	84	
wet II	70.5	10.3	222	34.7	•3		120	78.8	37.2	38.0	88	
40-nin, run		••	N	24.9	.01	- 44	. '		27.3	38.6	63	
wet III	63.5	48.7	24.0	u	44		72.5	73.4	27.3	34.8		
	A	- · · ·		L		L			· · · · ·			

Individual values for body unight, anyon blake lines $\sqrt{D_{\rm p}}$ in the Work Coparity Yest and everage $\sqrt{D_{\rm p}}$ during running) and performance relative to the usek expansivy solubmized in WCT 2 of the experimental control corts (pro and past Spariases).

***** ______ WCT III. The improved work capacities of Subjects C and D were also expressed in greater total energy expenditures (See Table 3). Thus, while the untrained subjects undoubtedly benefited from the drug, the application of Spartase in the two subjects who were trained for peak performance in running appeared to upset slightly the adequate adjustments for severe physical efforts. These differences in response were certainly not the result of train ing or motivating factors nor, apparently, the result of climatological factors (See Table 1) In the case of Subject C, all experimental worl was done in the laboratory under controlled environmental conditions, and in the other experiments temperature, humidity and solar radiation were nearly the same.

TABLE 3

	CONTROL EX	PERMENTS	SPARTASE EX	PERMENTS
	Entry Esp.	Curotion	Course Cas.	Duroties
SUBJECT	bcol,		beel,	blin,
A) WELL	2001	170	. 1979	160
B) TRAINED	1965	164	1947	190
	2032	180,5	1963	169
C) LESS -	1206	139	1304	147
DI TRAINED			1915	196
AVERAGE ;	1410	143	1603	161,6

ESTIMATED TOTAL ENERGY EXPENDITURE

TILT TABLE TEST

The orthostatic tolerance tests revealed similar reaction patterns in all four subjects. The group averages of blood pressure and pulse rate, presented in Figure 4, show that, in the "control" experiments, the pre-exercise tilting from the supine position to a 60-degree incline caused a slight fall of blood pressure from an average of 124/82 to 120/83 mm Hg accompanied by a rise in pulse rate from 59 to 67 beats per minute. After the fatiguing exercise, during a period of recovery, the changes were more impressive, the blood pressure declining from 118/83 to 93/76 mm Hg while the pulse rate increased from 103 beats per minute to *128 as an average for the 7-minute period of tüt,

Thus, orthostatic tolerance appeared definitely affected by physical fatigue. In the "Spartase" experiments the peripheral neurocirculatory responses to the postural changes were nearly identical. This might indicate that in both experimental situations physical fatigue had developed to an identical extent, or that the tilt table tests were not specific enough for detecting more subtle differences in accumulated fatigue.

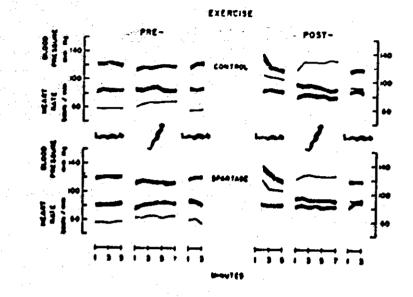
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Figure 5 shows a representative recording of the ECG taken at rest and during exercise before and after Spartase. There was no indication of changes in the ECG that might be attributable to Spartase.

The fatigue effect occurring with work in each series of tests is apparent in comparing the 10th minute tracings for WCT I and III. The WCT III tracing made at a metabolic rate of 8 times the resting level closely resembles the peak minute tracings of WCT I made at 12 times the resting metabolic level.

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Igue: 4. - Average systelie and disatelie bland previoure and pulse rates of 4 subjects during the orthestatic tolerance tests, before and after exercise, in the Control and Spartase series of experiments.

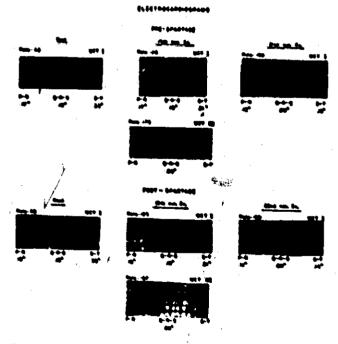


Figure 5. - ECG tracings obtained during work capacity tests in Control and Spastane series of experiments.

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DISCUSSIONS

Improved swimming performances of rats treated with Spartase were reported by Laborit, et al.,¹⁰⁰ and Rosen et al.¹⁰¹ The latter group of investigators made the following observations: The performances observed in 36 control rats appeared to divide them into two major groups, one of lower and one of higher survival capability in endurance swimming. In another experimental series with 36 rats treated with Spartase, this differentiation did not occur and the mean swimming time of this group exceeded that of the control rats. The investigators concluded that the animals of initially low performance capacity were favorably affected by this drug.

A similar response pattern seems apparent in this study with humans. A fatigue mitigating effect of Spartase was observed in the two untrained subjects when their cardiorespiratory and metabolic functions were severely taxed in extended physical efforts. After the administration of Spartase, Subjects C and D expended 100 to 300 kilocalories of additional energy under conditions of near-exhaustion and still scored considerably better in the final performance tests. The two-trained subjects, on the other hand, showed only slight quantit tive changes in performance and no qualitatic changes in the fatigue pattern of function response to the test work. Whatever ro Spartase may play in intermediary metabolisr it contributes nothing to the metabolic capabiity of the trained individual. Evidently, the trained organism has attained a point of opt mum coordination of functional and metabol adjustments that cannot advantageously be affected by this drug.

We can only speculate on the mechanism involved in mitigating the fatigue of the ur trained individuals. A more economical respira tory action is a possibility suggested by th work of Laborit and others."" They found reduction of CO, in plasma and expired al of hypercaphic dogs treated with magnesiun and potassium aspartates. This reduction sup posedly occurred as CO, and NH, were utilized In the ornithine cycle. In the case of Subject C on whom periodic measurements of CO, is expired air were made, there was an indication of reduced CO, production after the administration of Spartase. This is shown in the data of Table 4. While these data are not conclusive, they are in the direction expected from

TABLE 4

EXPIRED VOLUME OF CARBON DIOXIDE

mi/kg/min ---- ,Subject C

• •	WC	i.	WC.	гш	WCT	
tila,	Pre-Sp.	Post-Sp.	Pre-Sp. Sa	Post-Sp.	Pre-Sp.	Post-Sp.
			•	í		
2	9.5	11,1	13.4	13.4	12.0	10.6
•	18.5	18.4	17.6	17.1	17.2	i6.4
10	24,2	24.0	26.0	23,5		
14	31.2	29,9				
	42,6	40,1				

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Laborit's work. Respiratory center activity during work might have been diminished because of lower blood CO, content. Greater economy in the respiratory effort did occur in the cases of Subjects C and D, following Spartase. Both subjects showed sizeable reductions in ventilation at identical workloads, indicating greater ventilatory efficiency since the oxygen requirements remained the same,

The limitations of this study preclude any generalizations about the anti-fatigue effects of Spartase. However, the results, showing a fatigue mitigating effect in some individuals, are of sufficient interest to justify a more detailed study of its role in affecting respiratory gas exchange and intermediary metabolism during prolonged severe stress,

The authors gratefully acknowledge the technical assistance of Wilbur L, Smith and Kamal Shanbour.

SUMMARY

Some experimental and clinical investigations have shown that Spartase — the potassium and magnesium salts of aspartic acid — has a mitigating effect on physical fatigue.

It was the purpose of this study to evaluate the effects of the drug on the work capacity of four men before and after episodes of physically fatiguing exercises, Work capacity was determined on the treadmilli using the standardized procedure of gradual minute-by-minute increases of slope at constant walking speed. The test was repeated after the subject had been running cross-country for a period of 60 minutes, and again after another such period of 40 minutes. In this way effects of fatigue upon functional adaptability to stress became apparent. After control data had been established, Spartase was taken orally in recommended dosages for two weeks, whereupon the same complex testing procedure was repeated.

The performances of two well-trained individuals appeared to be unaffected by the drug. Two other individuals, who did not train regularly appeared to benefit from the Spartase medication. After Spartase these subjects expended 100-300 kilocalories of additional energy under conditions of near-exhaustion, and still scored considerably better on the crucial last performance tests.

The results indicated that Spartase was effective in mitigating physical fatigue in untrained individuals engaging in strenuous work. It appeared to have no effect on trained individuals.

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Givid Aeromedical Research Institute, Federal Aviation Agriney, Ohlahoma. City, Ohlahoma. CAHI Report 63-12. THE MITICATION OF PHYSICAL FATICUE WITH "SPAMITASE" by Francis J. Nagle, Ed.D., Bruno Bulke, M.D., Richard V. Canalen, Ph.D. and Audie W. Davis, Jr., M.D.	 Stress Physiology Stress Pharmacology Physical Fames 	Chil Arrawdicil Ressurts Instress, Federal Avation Arraw, Oklabona Ciry, Oklabona, CALI Report 63-12, THE MITICATION OF PHYSICAL YATICUE WITH "SPARTASE" by Francis J. Nicle, EdD., Bruno Bulle, N.D., Richard V. Canden, Ph.D. and Andio W. Davis, Jr., N.D.	1. Stree Physical 2. Stree Physical 3. Physical Fatters 3. Physical Fatters
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Phurmacellegical and claured observations have fulficated that Spiratuse - the superite area who of potantian and magnetian - taken part in the intermediary metabulan and medicated physical fangue. In this study attempts were made to evaluate effects of the drug on work copierly before and after epidodes of physically fattyrang constructs. Work expering a fatter physically fattyrang constructs work expecting a dis- physically fattyrang constructs with period of 60 memory, and again after mucher such period of 40 minutes to the way effects of fattore upon functional adaptivity to the upbyradi date for two works whereapon the mass better protected the fattores performed a dispetibility to protected the for two works whereapon the mass better protected the enduance performance of mattered fattores protected the enduance performance of mattered fattores anyoned the enduance performance of mattered fattores.		Promotogical and chared observations have indicated the Sparture - the anjustic and subto of polynomic and margenesis theorem is the merimentary metabolism and medication physical fragme. In this work expressive weak and after sparture effects by a dist days can weak copiesty before and after sparture dis- physically functions cannot with capacity we descrimined by a subject had here meaning the constrained after the subject had here meaning transmitted after the university for a partial of 60 meaning and after meaning transmitted after the university for a partial of 60 meaning after a flagree upon functional aliquitability in the university of the results weak printed of 40 meaning the university of the results weak for the functional provided due respected. The meaning the sparture due to excluse the results of hybertic due to the sparture provided the reductors professions of university for the sparture of meaning the results of the sparture provided the reductors professions of university for the sparture of meaning the results of the sparture provided the reductors professions of university in the provided the reductors professions of university in the provided the reductors professions of university in the provided the reductors professions of university in the results.	