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Physical Training Under the Influence of Beta Blockade in Rats: Effect on Adrenergic Responses

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Summary. Rats were trained by daily swimming or running exercises with and without daily propranolol injections. Both training methods resulted in cardiac enlargement, but only swimming exercise caused hypertrophy of the brown adipose tissue. These changes were antagonized by beta blockade. The size of the adrenals reflected the stress of the treatments, but other known stress parameters, such as the size of the thymus or sexual organs dit not. Only swimming training without beta blockade sensitized the rats to the calorigenic action of noradrenaline. The cooling rate of the rats in water, when taking into account the insulative capacity of the body, was decreased in swimming-trained as well as in propranolol-treated rats but increased in running-trained rats. The latter two changes may be due to circulatory alterations, while the delayed body cooling in swimming-trained rats probably results from increased heat production capacity. Training-induced resting bradycardia and enhanced tachycardic response to isoprenaline were observable only in the animal groups trained without beta blockade. The pressor response to noradrenaline tended to be higher in the trained groups and the propranolol-treated group than in the controls and was smaller in the animal groups trained under the influence of beta blockade. On the other hand, the hypotonic response to isoprenaline was smaller in the propranolol-treated and running-trained animals. The results emphasize the importance of the sympathetic nervous system in the adaptation of an organism to physical training.

Key words: Swimming training – Running training – Adrenergic responses – Cold tolerance – Prolonged beta blockade

Intense exercise causes activation of the sympathetic nervous system leading to an increased release of noradrenaline from the sympathetic nerve endings and adrenaline from the adrenal medulla (Cannon and Britton, 1925; Ashkar et al., 1968; Häggendal et al., 1970; Gordon et al., 1966). Prolonged activation of the sympathet-

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ic nervous system is known to occur in exposure and acclimation to cold (Leduc, 1961; Gordon et al., 1966). This activation can be simulated by repeated injections of noradrenaline, noradrenaline-treated rats (LeBlanc and Pouliot, 1964; LeBlanc and Villemaire, 1970; Vallierès et al., 1972; Hsieh and Wang, 1971; Harri, 1978b) demonstrating many of the characteristics of cold-acclimated animals. These rats, like cold-acclimated animals, have a larger oxygen consumption and rectal temperature increase in the cold, an increased resistance to low temperatures, an enlarged heart and increased brown adipose tissue, and an increased sensitivity of adrenergic beta receptors associated with a decreased sensitivity of alpha receptors (Harri et al., 1974; Tirri et al., 1976).

This study attempts to elucidate whether sympathetic activity levels induced by repeated periods of exercise are enough to induce changes similar to those produced by repeated noradrenaline injections or by the increased sympathetic activity associated with cold acclimation. The rats were trained by running and swimming exercises. Some of the animals performed their training programs under the influence of beta blockade, which was used to reduce sympathetic influence.

Exercise is known to elicit marked changes in many blood hormones including cortisol, growth hormone, sex hormones, luteinizing hormone, plasma renin activity, and aldosterone (Kuoppasalmi et al., 1978). Furthermore, it is known that small rodents are sensitive to stress situations; the hormonal imbalances resulting from long-lasting stress situations lead to an enlargement of the adrenal cortex, to an impairment in immune responses as evidenced by a reduction in the size of the thymus, and to impairment of the reproductivity as evidenced by reduction in the size of the sex and accessory sex organs. To see whether the stress produced by forced exercise is sufficient to induce changes in the stress characteristics mentioned above, the size of the adrenals, thymus, testis, and seminal vesicles was evaluated after the training and/or drug treatment period.

Material and Methods

Male rats of a Wistar/Af/Han/(Han 67) strain were housed in groups of 3 or 4 in plastic cages and maintained on a diet of standard laboratory chow (Hankkija, Finland) and water. The room temperature was kept at 19 ± 1° C.

The rats were divided randomly into 6 groups. Group C was the control group, which was injected daily with a physiological saline-glycerol (3 : 2) mixture. Group P rats were injected daily with 10 mg propranolol hydrochloride (ICI, England)/kg. Group R animals were trained on a motor-driven treadmill according to the steady state running program of Baldwin et al. (1977); the velocity and slope of running were 0.45 m/s and 19°, respectively. The initial running time was 10 min and this was extended by 3 min daily until the animals ran continuously for 1 h. Group S was composed of animals trained by daily swimming in water at 37° C. The initial swimming time was 1 h and this was extended by 15 min daily until the animals swam continuously for 3 h (Harri, 1978a). The rats belonging to groups R+P and S+P were injected with 10 mg propranolol/kg immediately before each running or swimming exercise. Propranolol was injected s.c. in a saline-glycerol mixture (3 : 2). The animals received the training regimes and/or injections five times weekly for the total duration of time indicated below.

Twenty-four hours after the 22nd to 24th injection and/or training treatment the cooling rate was measured for the rats which were swimming in water at 25° C (Dawson et al., 1970; Harri, 1978b). To determine the insulative capacity of the rat, the cooling rate was also measured for the dead animal body, which has no heat production. The body was first heated to 38° C and then immersed into water

at 25° C. The cooling rate of the experimental groups was related to that of rats of various sizes in order to evaluate the dependence of the results on body size.

The colonic temperature response to injected noradrenaline (0.5 mg/kg i.p.) was determined at a thermoneutral temperature of 28° C 24 h after the 26th to 28th injection and/or training regime (LeBlanc and Villemaire, 1970; Harri, 1978b). Colonic temperatures were obtained with a thermocouple inserted to a depth of 4 cm, and recorded on an Ellab TE 3 (Copenhagen) potentiometer.

The heart rate and blood pressure responses to a beta-adrenergic drug, isoprenaline, and to an alpha-adrenergic drug, noradrenaline, were measured 24 h after the 34th to 40th injection and/or training treatment. The animals were anesthetized by veterinary Nembutal (pentobarbital sodium, Abbott), 50 mg/kg injected i.p. One carotid artery was cannulated for blood pressure measurement and the opposite jugular vein for the drug infusion. The body temperature of the animals was maintained at $37 \pm 1°$ C with the aid of a heat lamp. Continuous measurements of heart rate and blood pressure were made with strain gauge transducer (Hewlett Packard 267 BC series), amplified with a carrier amplifier (Hewlett Packard 8805 B), and recorded on paper by an ink-jet writing recorder (Elema, Schönander, Mingograph 34). The heart rate was obtained from the blood pressure recordings. The significance of the difference between group means was evaluated by Student's *t*-test. The significance of the changes in the heart rates and pressures was calculated with the paired comparison test, a modification of the *t*-test (Daniel, 1974).

Results

The results in Table 1 show that propranolol treatment as such did not reduce the weight gain or food consumption of the rats. However, all the trained rat groups gained significantly less body weight than did the controls. This reduced weight gain tended to be more obvious in the rat groups trained under the influence of beta blockade. In running-trained groups the reduced weight gain was associated with a reduced food intake, while the swimming-trained rats gained less weight in spite of their increased food consumption. Both training regimes resulted in cardiomegaly, this being greater for swimming than for running. Propranolol treatment decreased the heart size and, when coupled with the training, impaired the development of cardiac enlargement. Although the size of the adrenals increased in all trained groups the changes in the size of thymus, testis or seminal vesicle were variable and did not show any systematic response to either training or to drug treatment or to both. However, swimming training, but not running training, induced an enlargement of the interscapular brown adipose tissue. On the other hand, propranolol injections reduced the size of this tissue when given alone, or decreased the enlargement of the tissue caused by swimming exercise.

Only swimming-exercised rats showed a hyperthermic response to noradrenaline test injections (Fig. 1). This response was less marked in the animal group which had received an equal amount of training but which had trained under the influence of beta blockade. In other groups, noradrenaline failed to cause hyperthermia. In the R + P group, a slight hypothermic response was seen instead.

Figure 2A shows the cooling constants for rats of different sizes when swimming in water at 25° C. The cooling constants were calculated according to the formula of

$$C = 2.3 \; d \log [(T_{B0} - T_A)/(T_B - T_A)]/dt \quad \text{(Morrison and Tiez, 1957)},$$

where T_B and T_A refer to body and ambient temperature, respectively. It can be seen at the cooling constant is greater for smaller than for larger rats. The values for the

Table 1. Body and organ weights in control, propranolol-treated, swimming- and running-trained rats, and in rats injected with propranolol always before the daily running- or swimming-training periods[a]

	Control	Propranolol	Swimming	Swimming + Propranolol	Running	Running + Propranolol
Initial body weight, g	265 ± 4.7	259 ± 5.2	257 ± 8.5	271 ± 6.1	270 ± 6.4	260 ± 8.1
Food consumption, g/rat	1081	1076	1132	1131	995	918
△ Body weight, g	82.0 ± 5.4	79.0 ± 5.6	47.5 ± 4.7[e]	35.0 ± 12.3[e]	51.1 ± 5.8[e]	48.7 ± 4.6[e]
Heart, mg/100 g	281 ± 3.8	256 ± 12[c]	462 ± 2.3[e]	295 ± 2.4	306 ± 4.9[e]	289 ± 4.7
Thymus, mg/100 g	152 ± 7.1	147 ± 7.4	174 ± 10.5	130 ± 9.9	119 ± 2.7[d]	99 ± 6.4[e]
Adrenals, mg/100 g	19.9 ± 1.0	20.6 ± 1.0	28.6 ± 1.5[e]	27.0 ± 1.6[e]	25.5 ± 0.8[e]	27.9 ± 1.9[e]
Testis, mg/100 g	1099 ± 24	1167 ± 25	1273 ± 27[d]	1326 ± 38[e]	1119 ± 45	1242 ± 20[e]
Seminal vesicle, mg/100 g	293 ± 10.3	331 ± 8.2[c]	332 ± 12.8	296 ± 19.3	311 ± 24.6	348 ± 19.1[c]
ISBAT, mg/100 g[b]	118 ± 5.6	80 ± 4.8[e]	141 ± 6.2[c]	126 ± 6.3	107 ± 5.1	86 ± 5.5[e]

[a] Each value is the mean ± S.E. of 10 animals

[b] ISBAT = interscapular brown adipose tissue

Asterisks mark those values which significantly differ from the controls: [c] $p < 0.05$, [d] $p < 0.01$, and [e] $p < 0.001$

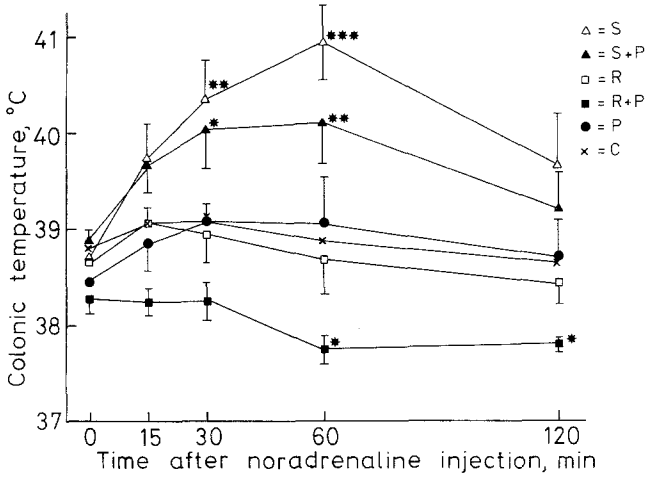

Fig. 1. The response of the colonic temperature to injected noradrenaline (0.5 mg/kg i.p.) at 28° C. C = control rats, P = propranolol-treated rats (10 mg/kg daily for 26 to 28 days), R = running-trained rats, S = swimming-trained rats. S + P and R + P indicate the rats injected with propranolol always immediately before the daily swimming or running trainings, respectively. Noradrenaline was injected at 0 min. Vertical bars indicate ± S.E. Asterisks mark those changes which significantly differ from the initial (0 min) value: $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$. 4 to 5 rats per group

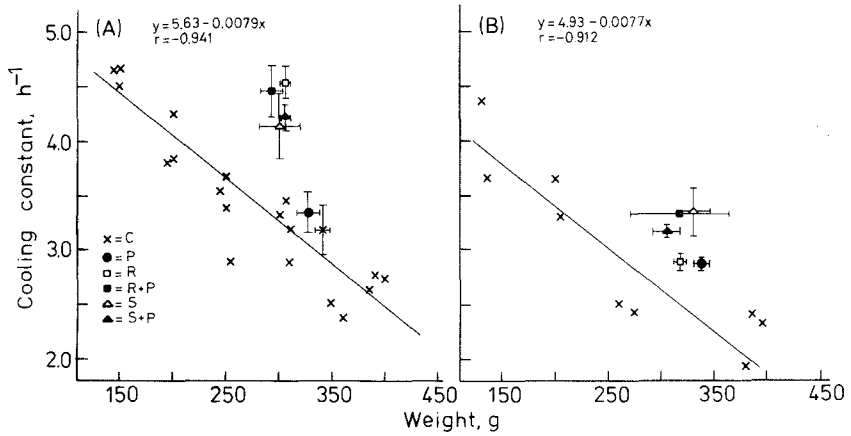

Fig. 2A—B. The dependence of the cooling constant on body size in rats swimming in water at 25° C (**A**), and in dead rat bodies initially heated to 38° C and then immersed into water at 25° C (**B**). The lines show the calculated regression lines which best fit the data. The symbols provided with vertical and horizontal bars indicating ± S.E. show the sample means of 3 to 5 animals belonging to the six different experimental groups used. They are explained in Fig. 1

control rats and for the propranolol-treated rats fit well to the cooling constant-body weight regression line. However, the cooling rate was significantly faster for the trained rat groups than could be expected from their body weight. A rapid body cooling may be due to impaired heat production capacity or to impaired insulative capacity of the body. In a dead animal body, when immersed in water, the rate of

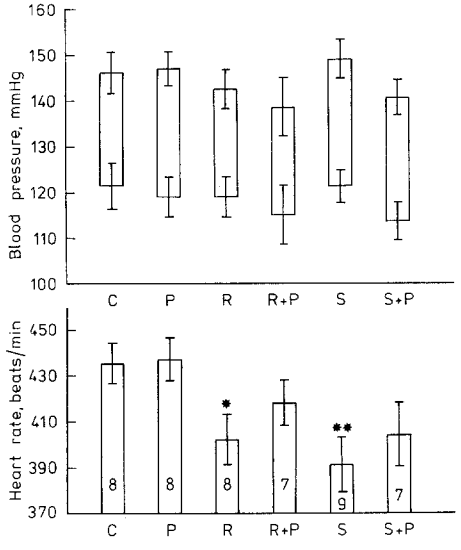

Fig. 3. The resting heart rates and blood pressures in pentobarbital anesthetized rats. In the blood pressure values, the top of the columns denote systolic and the bottom diastolic blood pressure. Vertical bars indicate ± S.E. The numbers inside the columns indicate the number of rats used. Asterisks mark those values which significantly differ from the control: $*p < 0.05$ and $**p < 0.01$. Other explanations as in Fig. 1, with the exception that the duration of the propranolol and/or training treatments was 34 to 40 days

body cooling is dependent only on the insulative capacity of the body. It can be seen from Fig. 2B that the cooling constant for the dead animal body also depends on the size of the animal. The slope of the regression line describing this dependence in dead animals is identical with that in living rats. In this case, too, the cooling constant for all trained rat groups was even greater than could be expected from their body size. This may be due to the fact that these animals were thinner than animals of the same size generally. In an attempt to evaluate whether their smaller insulative capacity could account for their rapid rate of body cooling during swimming, the cooling constant of the dead animals was related to that of the living. This can be done only roughly, because the same individual animals were not used for both tests. For the control animals the ratio of the cooling constants of dead/living animals is of the magnitude of 0.755. The ratio for the R + P and S + P groups, 0.749 and 0.753, respectively, is thus of the same size as for the controls. However, for the R-group the ratio is only 0.638. This means that their cooling rate was faster than could be expected from their insulative capacity. On the other hand, the ratio is 0.857 and 0.813 for the P- and S-group, respectively, indicating that their cooling rate was slow in relation to their insulative capacity.

As can be seen in Fig. 3, none of the treatments used influenced the resting blood pressure values of the rat. On the other hand, the resting heart rate was significantly decreased in both the animal groups which performed their exercises without the drug. In the animal groups trained under the influence of beta blockade no training bradycardia was observed.

Figure 4 shows the heart rate responses of anesthetized rats to isoprenaline and noradrenaline. The slight bradycardia caused by noradrenaline was variable, and no significant differences between the experimental groups could be evidenced. The heart rates after isoprenaline infusion rose to comparable levels in all experimental groups. However, since the resting heart rate was slower in the animal groups trained without beta blockade, the increase in heart rate caused by isoprenaline

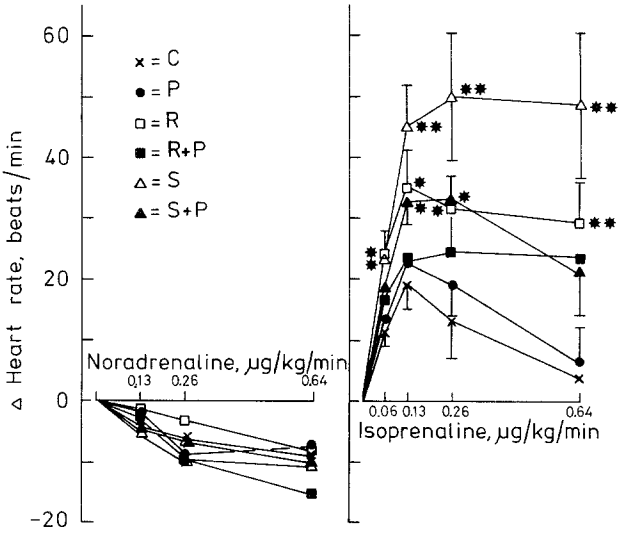

Fig. 4. Effect of noradrenaline and isoprenaline infusions on heart rate in anesthetized rats. Responses that differ significantly from controls are marked by asterisks: $*p < 0.05$, $**p < 0.01$. Other explanations as in Fig. 1, with the exception that the duration of the propranolol and/or training treatments was 34 to 40 days. The numbers of animals are identical to those presented in Fig. 3

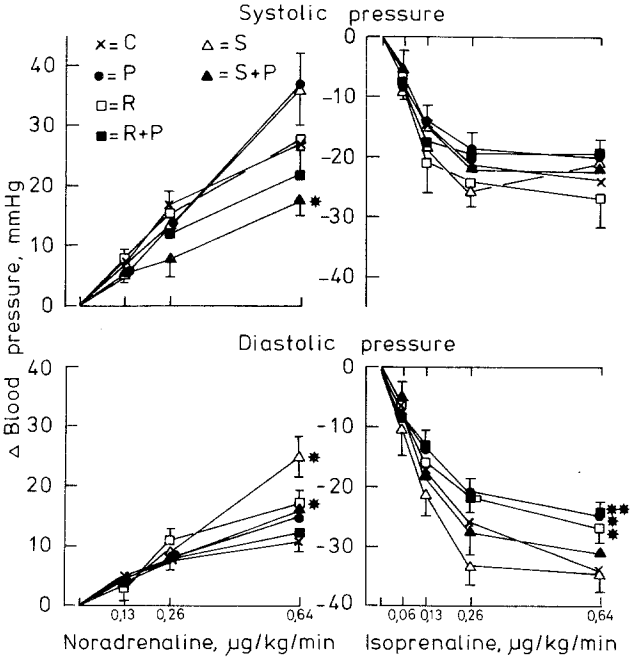

Fig. 5. Diastolic and systolic blood pressure responses to noradrenaline and isoprenaline infusions in anesthetized rats. For other explanations see Fig. 4

infusion was significantly greater in these groups than in the controls. Furthermore, due to the higher resting heart rate, the tachycardic response to isoprenaline was smaller in the animal groups which performed their training sessions under the influence of beta blockade.

Figure 5 shows that the pressor response of the systolic blood pressure to noradrenaline tended to be greater in the P-, S-, and R-groups and smaller in the R + P- and S + P-groups than in the controls. However, only the last mentioned change was significantly different from the control. Furthermore, the response of the diastolic blood pressure was significantly greater in the S- and R-groups.

Unlike noradrenaline, isoprenaline infusion caused a marked drop in blood pressure. The drop of the systolic blood pressure was comparable in all experimental groups while the hypotonic response of the diastolic blood pressure was significantly smaller in the P-, R-, and R + P-groups as compared to the control group.

Discussion

The reduced weight gain in the trained rat groups is a well known phenomen; it can partially be explained by the reduced food intake in the running-trained rat group. Beta blockade alone did not influence the weight gain or food intake of the rats. However, in the R + P-group both parameters were reduced. The swimming-trained rats, whether trained with or without beta blockade, gained less body weight in spite of increased caloric intake. This indicates that the energy demand of swimming exercise was higher than that of the running exercise used. The reduced food intake in running-exercised rats (Thomas and Miller, 1958; Stevenson, 1966) and the increased food intake in swimming-trained rats (Baldwin et al., 1975) have been reported earlier, but no explanation of this difference has been put forward.

The enlargement of the adrenals in all trained groups, whether trained with or without beta blockade, can be regarded as an indication of the stress of the treatments. However, those other stress parameters, the size of the thymus, testes or seminal vesicles, did not respond to the treatments used in such a way that they could be used as an indication of the magnitude of the stress caused by training and/or drug treatments.

It is generally known that strenuous physical training leads to increased oxidative capacity in muscle, while prolonged beta blockade tends to decrease it (Harri, 1977). For this reason, it was to be expected that trained rats would be more resistant to body cooling in cold water and that rats pretreated with beta blockers would be less resistant. Indeed, improved cold tolerance has been found in swimming-exercised rats (Harri and Valtola, 1975). Since the cooling rate of animals depends on both heat production capacity and the insulative capacity of the body, and since all the trained rat groups were thinner than the controls or animals treated with propranolol only, it was necessary to analyze their respective insulative capacities. In dead animals immersed in water the rate of body cooling depends on the insulative capacity of the body only (Dawson et al., 1970), and this rate can be used as a rough estimate of it. In this study the ratio of cooling constants of dead/alive animals was used as a rough estimate of heat production capacity. It was increased in swimming-trained rats but not in animals pretreated with propranolol in combination

with swimming exercises. This finding is consistent with other results obtained, i.e., more marked activation of brown fat and non-shivering thermogenesis in the S-animals than in the S + P-animal groups.

On the other hand, the decreased ratio in the R-group and increased ratio in the P-group are not consistent with the above mentioned hypothesis. However, it has to be kept in mind that the cooling rate of a dead animal is dependent only on the insulative capacity of body tissues. In a living animal the distribution of blood circulation greatly affects the insulative capacity of the body. It has been found that prolonged beta blockade may lead to compensatory supersensitivity of alpha-adrenoceptors (Harri and Pelkonen, 1978). This may induce increased vasoconstrictor activity in the body surface of these animals resulting in reduced heat loss, and, accordingly, in a higher dead/alive cooling constant ratio. By contrast, running-trained rats maintain a higher skin temperature when exposed to cold temperature (Strømme and Hammel, 1967). This may indicate a higher vasodilatatory activity in their body surface and also a higher rate of body cooling. This result, together with the changes concerning brown fat and non-shivering thermogenesis, may indicate a basic difference between swimming and running training. The former leads to intensification of heat production and/or conservation activities because of threatening hypothermia. In the present study the high water temperature (37° C) prevented hypothermia during the swimming period, but an increased demand on thermoregulatory machinery was evident when the animals were placed at a room temperature of 19° C with their wet fur. In many cases a violent muscular shivering was required to keep their body temperature at a normal level after swimming. Running training, on the other hand, tends to activate heat losing mechanisms to protect the body against excess hyperthermia following vigorous physical exercise in air. It is interesting to note that beta blockade associated with training periods tends to oppose both the increased cold tolerance following swimming training and the increased heat loss capacity resulting from running training.

Increased release of catecholamines associated with both cold acclimation and repeated injections of exogenous noradrenaline produce cardiac enlargement, hypertrophy of brown adipose tissue, increased calorigenic sensitivity to noradrenaline, increased tolerance to cold as measured by the swimming time in cool water, resting bradycardia, and increased tachycardic response to isoprenaline (Harri and Valtola, 1975; Harri, 1978b; LeBlanc and Pouliot, 1964; LeBlanc and Villemaire, 1970; Vallières et al., 1972; Hsieh and Wang, 1971). All these changes were observable in swimming-trained rats, while only cardiac enlargement, resting bradycardia, and increased tachycardic response to isoprenaline were found in running-trained rats.

Prolonged beta blockade failed to induce any of these changes. By contrast, it decreased the size of the heart and brown fat. In addition, when combined with exercise training prolonged beta blockade abolished or at least hampered the development of the training induced changes mentioned above. Since beta blockade also antagonizes the changes produced by repeated noradrenaline injections (Harri, 1978b), it is reasonable to conclude that it is the increased release of noradrenaline associated with exercise periods that is responsible for the changes observed. This assumption is supported by the results of Sigvardsson et al. (1977), which show that, after chemical sympathectomy with 6-hydroxydopamine, rats failed to adapt to endurance training or did so only to a decreased extent.

If the sympathetic activity bouts associated with exercise periods are responsible for the changes observed, it is difficult to understand why these activity periods enhanced calorigenic sensitivity to noradrenaline or increased the size of brown fat in swimming-exercised rats but not in the runners. Since all the changes obtained tended to be more marked in swimming-trained rats, the greater endurance of the swimming exercise as compared with running exercise could be one possible explanation. Another explanation is the demand on thermoregulatory capacity caused by swimming. Although the body temperature of the animals did not change during and after the swimming periods (Harri, 1978a) the animals do need much extra heat after cessation of the swimming programs, because their fur is wet and the insulative capacity of fur is decreased when it is wet. This is sufficient to trigger the thermoregulatory machinery including the sympathetic nervous system, thus placing more demands on the sympathetic nervous system than does exercise alone. Prolonged activation of the sympathetic system is known to activate non-shivering thermogenesis, which is demonstrated by the increased calorigenic response to noradrenaline (Janský, 1973). It has also been found that short-term activation, although repeated, does not lead to increased calorigenic response to noradrenaline (LeBlanc, 1969). For this reason, it is possible that even very marked sympathetic activation during running exercise periods is – because of its short duration – not enough to activate non-shivering thermogenesis. However, it is more difficult to explain why the size of the brown fat, as observed in this study and earlier by Dawson et al. (1970), did not change in response to running training, because even very short sympathetic activity bouts associated with repeated cold-exposures is sufficient to increase the relative weight of this tissue in mice (Tarkkonen, 1971).

The pressor response to noradrenaline was slightly increased in both animal groups trained without beta blockade. A similar response has been observed in trained men (LeBlanc et al., 1977). Since repeated noradrenaline injections lead to decreased pressor response to noradrenaline (Harri, 1978b; Vallières et al., 1972) this phenomenon cannot be explained solely by the increased noradrenaline turnover mechanism. However, the fact that prolonged beta blockade prevented or reduced this change supports the role of the adrenergic mechanisms. On the other hand, increased pressor response to noradrenaline also results from 6-hydroxydopamine treatment (Krakoff and Ginsburg, 1973), which treatment, in fact, reduces the adrenergic influence.

Prolonged beta blockade alone and in combination with running exercises as well as running exercises alone reduced the hypotonic responses to isoprenaline. Since swimming exercise did not induce this change, a common training-dependent change cannot explain the phenomenon, and since beta blockade associated with swimming exercises did not lead to this change, beta blockade cannot give a satisfactory account for it. Vallières et al. (1972) found a reduced hypotonic response to isoprenaline in noradrenaline-treated rats, while Harri (1978b) found no change in this response after a similar treatment. Furthermore, in accordance with the present study Harri (1978b) also found a reduced hypotonic response to isoprenaline in rats treated chronically with a beta blocker. Thus, it is possible to find support both for the hypothesis that increased sympathetic activity is responsible for this change, and also for the altered response to noradrenaline, and that a reduced sympathetic influence could be the mechanism involved in these changes. Since the regulation of

blood pressure is a net effect of many mechanisms, an apparently similar change in it may result from one or another factor.

At present we can only conclude that physical training influences the sensitivity of an organism to catecholamines, and the effect of running training differs from that of swimming training. Apparently the alterations in activity of the sympathetic nervous system associated with training play an important role in these changes. Their final mechanisms have, however, to be clarified by further, more detailed experiments.

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