Heat acclimation: role of norepinephrine in the anterior hypothalamus

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CHRISTMAN, JOHN V., AND CARL V. GISOLFI. *Heat acclimation: role of norepinephrine in the anterior hypothalamus.* J. Appl. Physiol. 58(6): 1923–1928, 1985.—The hypothesis that anterior hypothalamic (AH) sensitivity to norepinephrine (NE) is altered by chronic exercise in the heat was tested in male Sprague-Dawley rats. Treadmill exercise 6 days/wk for 3 wk at 21 m/min was performed at 23°C (control; C) or at 35°C (heat acclimated; HA), progressing from 20 to 50 min/day in 2 wk. Time for core temperature (T_{co}) to rise from 39.5 to 40.5°C during a heat-tolerance test after conditioning increased ($P < 0.05$) in the HA group. To test for a change in AH sensitivity, the change in T_{co} to 2-, 5-, 10-, 20-, and 40-μg doses of NE injected bilaterally into the AH was determined after conditioning. Dose-response regression lines showed that exercise in the heat increased the slope and shifted the T_{co}-NE dose relation to the left. In a separate series of experiments on 6 sedentary(s), 10 C, and 10 HA animals, the amounts of NE, dopamine, and 3,4-dihydroxyphenylglycol (DOPEG) were determined by high-pressure liquid chromatography in the AH, median preoptic area (PO), cortex, and cerebellum after 9 wk of conditioning. Results showed that in the PO there was a significant increase in NE and DOPEG in the HA vs. C group and a trend of increasing NE from the S to C to HA groups. The data indicate that exercise in the heat increases NE-induced peripheral heat-dissipating capacity and increases catecholamine storage in the PO.

exercise; rat; temperature regulation; hypothermia

ACCLIMATION TO WORK IN THE HEAT produces both central and peripheral changes that enable an animal to function under conditions of high thermal stress. Although the peripheral changes are well documented (9, 23), evidence supporting an alteration in central nervous system (CNS) activity is inconclusive. In the rat, the physiological responses to chronic heat exposure include a reduction in basal metabolism (1), an increase in salivation (16), and a slower rate of rise in core temperature during a standard heat-tolerance test (4).

If a central change in thermoregulatory function were to accompany heat acclimation, the most likely area of the brain to be affected would be the preoptic anterior hypothalamus (POAH), since the POAH is acknowledged to play an integrating role in the control of thermoregulatory effector responses (14). Furthermore, this area of the brain contains a high concentration of noradrenergic and dopaminergic terminals (7), which have been implicated in heat dissipation. Lesioning catecholamine-containing neurons in the AH with 6-hydroxydopamine impairs thermoregulation in the heat (22); and blocking α-adrenergic or dopamine (DA) receptors in the AH with phentolamine or pimozide, respectively, produces a significantly greater hyperthermic response to exercise compared with controls (11, 12). Microinjection of norepinephrine (NE) or DA into the POAH produces a dose-related hypothermia (11, 12), but similar injections into the posterior hypothalamus elicit no thermoregulatory response (8). Exposure to heat, but not to cold, causes the release of NE from the AH and median PO area (6, 21).

We previously reported that a 10-μg dose of NE at rest in a 22°C environment produced a significantly greater hypothermia compared with controls (4). Because only one dose of NE was investigated in that study, the proposed increase in hypothalamic sensitivity post-heat exposure was inconclusive. The purpose of this investigation was to confirm and extend those observations by determining dose-response curves relating the change in core temperature (T_{co}) with NE dose for control-exercised and heat-exposed animals. The rationale was that an altered slope of the regression line for T_{co} vs. NE dose would indicate an augmented effector response to a given central drive (peripheral change), whereas a shift in the dose producing one-half the maximal response (K_a) or a parallel shift in the T_{co}-NE dose relation would indicate a change in drug-receptor interaction, thus providing evidence for a central change. We further hypothesized that repeated elevations in T_{co} and stimulation of heat dissipation during exercise in the heat would reduce the levels of catecholamines in brain areas known to activate heat loss mechanisms. Thus a second purpose was to determine whether heat acclimation would influence catecholamine levels in the POAH. NE, its direct precursor DA, and one of its two major metabolites in the rat AH, 3,4-dihydroxyphenylglycol (DOPEG) (25), were measured.

METHODS

Dose-Response Experiments

Twenty-one male Sprague-Dawley albino rats initially weighing 262 ± 6 g were provided with Purina rat chow and water ad libitum and were maintained on a 12-h light-dark cycle. Experiments were performed according to "Guiding Principles in the Care and Use of Experimental Animals" and were carried out during the first few hours of the light cycle. For 2 wk before surgery,

each rat was handled 10 min/day and exercised 15 min every other day. During the second week of treadmill familiarization, the rats were accustomed to a rectal probe [Yellow Springs Instrument (YSI) 402] inserted 8 cm into the colon and taped in place to measure T_{co}. The rats were behaviorally conditioned to lie facing forward with their tails extended when resting on the treadmill by tugging lightly on the temperature probe if they moved. This positioning assured equal tail skin exposure for heat dissipation during all testing.

Surgery. Bilateral 23-gauge stainless steel guides were stereotaxically implanted above the AH as before (11) using the coordinates of Pellegrino and Cushman (26): 0.7 mm anterior to bregma, 0.75 mm lateral to the midline, and 6.5–7.0 mm below the dura.

Microinjections. NE (*l*-arterenol bitartrate, Sigma, St. Louis, MO) was dissolved in artificial cerebrospinal fluid (ACSF) that had electrolyte concentrations of 127.7 mM Na^+, 134.5 mM Cl^-, 2.5 mM K^+, 1.3 mM Ca^{2+}, and 0.9 mM Mg^{2+} (20). Solutions were prepared in pyrogen-free glassware. Injections were made bilaterally, 0.5 μl injected in 30 s into each AH nucleus for a total dose of 10 μg. T_{co} was recorded continuously on a Texas Instruments Multiriter chart recorder to 0.1°C.

Starting 4 days after surgery, NE (10 μg) injections were made every other day. This schedule was chosen because our previous experience had shown that daily NE injections caused the rats to become irritable and difficult to handle. No behavioral difficulties occur with injections spaced two or more days apart. Injections were made initially 7 mm below the brain dura. If T_{co} did not begin to decline within 3 min and drop at least 0.6°C below the initial T_{co}, the next injection was made 0.5 mm deeper. Once an adequate response was obtained, it was verified by another injection at the same site 2 days later.

Heat-tolerance test and exercise conditioning. In all treadmill tests and conditioning runs, temperature and airflow within the treadmill were controlled by an Amana heater-air conditioner regulated by a YSI temperature control unit. After the site-determination tests and when the animals had run for at least 3 days after surgery, a heat-tolerance test (HTT) was performed. The rats rested on the treadmill at 23°C, with an airflow of 20 m/min, until T_{co} had stabilized for at least 10 min (total resting time ~30 min). The treadmill was then started, and ambient temperature was raised to 35°C in 2 min. The animals ran at 21 m/min until their T_{co} reached 40.5°C (4).

Following the HTT, the animals were assigned to the control group (n = 10) or the heat-acclimated group (n = 11) so that the mean time for T_{co} to reach 40.5°C during the HTT and the mean T_{co} decline in response to 10 μg NE were equal for both groups. Heat-acclimated animals exercised at 33–37°C, whereas control animals exercised at 23°C. Conditioning proceeded as described previously (4).

Dose-response testing. After 22 days of conditioning, the HTT was repeated and dose-response injections were begun. Microinjections of 2, 5, 10, 20, and 40 μg NE were made every other day, alternating low and high doses. The 10-μg dose was given first to establish if a change from the preconditioning response had occurred. A second 10-μg injection was made before the last remaining dose to verify that the responsiveness of the site was unaltered by the repeated injections. Treadmill exercise continued during the 14-day injection period. On injection days, the animals exercised several hours after the injection was made.

Histology. When testing of all animals was completed, the injection sites were labeled with methylene blue dye, and the brain was perfused with formaldehyde solution, removed, sectioned, stained, and examined histologically. All sites were identified as being within the AH as defined by Konig and Klippel (18).

Endogenous Catecholamines

Handling and treadmill familiarization of animals were the same as described above. Initial weight was 267 ± 5 g. Following the HTT, three groups of animals with equal mean times to reach a T_{co} of 40.5°C were formed: six sedentary rats (S), which were not exercised; 10 control rats (C), which exercised at 23°C; and 10 heat-acclimated rats (HA), which exercised at 33–37°C. The C and HA groups were made larger to allow for possible attrition during the conditioning program. Conditioning was for 9 wk to maximize the effects of the heat. After the final HTT, both groups exercised for 2 additional days at their respective temperatures to offset any effects of the HTT on brain catecholamines in the C group.

Tissue sample isolation. One day following the last conditioning session, the animals were killed. As soon as pentobarbital sodium anesthesia (50 mg/kg ip) had induced light sedation, the animals were decapitated. Within 4 min the brain was removed and frozen in liquid nitrogen. Samples were stored at −70°C until analyzed.

To assess general brain adaptation of catecholamines during heat exposure, 80- to 100-mg samples were taken of the cerebellum as an area involved in movement control and of the frontal cortex as an area not involved extensively in movement control. For the PO, the lateral spreading of the anterior commissure pars posterior was used as the rostral limit (matching the 7,470-μm section in the Konig and Klippel atlas). A central punch 2.5 mm in diameter and 1.0 mm thick was taken for the PO area, with an extrapolated line between the anterior commissures as the upper limit of the punch. The next caudal 1.5 mm was then punched out for the AH, using the fornices as the dorsal limit for a central 2.5-mm punch.

Sample analysis. Endogenous catecholamines were analyzed with reverse-phase high-pressure liquid chromatography (HPLC) using electrochemical detection. Detector flow cell electrode potential was 0.75 V, operating in oxidative mode.

Catecholamines were extracted from brain tissue homogenate by adsorption onto aluminum oxide (alumina). The internal standard 3,4-dihydroxybenzylamine (DHBA) was used because its dihydroxyphenol group absorbs to alumina as do natural catecholamines. The catecholamines were desorbed into a 0.10 M perchloric acid with 0.40 mM sodium bisulfite solution. This mixture was injected onto the HPLC after filtration through

a 0.2-μm pore filter. Retention volumes were DOPEG, 5.7 ml; NE, 7.6 ml; DHBA, 17.7 ml; and DA, 32.6 ml.

The amount of each catecholamine (CAT) in the tissue sample was calculated using the following formula

$$\text{ng CAT/g tissue} = \frac{\left[\frac{\text{CAT peak height}}{\text{DHBA peak height}}\right]\left[\text{ng of DHBA added}\right]\left[\frac{\text{(peak height/ng DHBA)}}{\text{(peak height/ng CAT)}}\right]}{\text{g tissue}}$$

All catecholamines produced a linear peak height vs. dose relationship, though the amperage elicited per nanogram of each catecholamine was different (Table 1). Percentage recovery from alumina (Table 1) was comparable to published data (31).

Catecholamine standard determinations showed 1% or less variation. The chart output was calibrated to 1%, and extrapolation to a third significant figure was possible to ~0.25% accuracy. Cerebellum and cortex samples ranged from 80 to 100 mg, measured to 0.1-mg accuracy, so catecholamines of these areas could be determined to the 1% accuracy limit of the HPLC system. PO samples averaged 4.0 mg, and AH samples averaged 6.1 mg. With measurement to 0.1 mg, the accuracy of their catecholamine measurements was therefore only taken to 2%.

Statistics. The dose-response data was normalized by dividing the temperature change to the five doses of NE after exercise conditioning by the temperature change to the 10-μg NE dose before conditioning. This normalization allowed each animal to serve as its own control and allowed measurement of the change due solely to experimental treatment. Means ± SE were calculated for all data. A split-plot analysis of variance was employed to determine if HA caused a shift in slope, efficacy, or K_a value of linear regression lines describing the T_{co}-NE dose relation (27).

Means ± SE were calculated for the catecholamine concentrations. An unpaired t test was used to evaluate intergroup differences. To test for trends in either direction, without assuming that the group means would fall in any particular order, the nonparametric rank-based Kruskal-Wallis test was used. However, it seemed likely that any changes, either increases or decreases, would occur in the order S to C to HA, the order of increasing heat stress during conditioning. Therefore, Spearman correlation coefficients and probabilities were also calculated. Statistical significance was accepted at the $P < 0.05$ level.

TABLE 1. *High-pressure liquid chromatography response characteristics of catecholamines*

Catecholamine	Retention Volume, ml	Peak Ht, nA/ng		Recovery from Extraction, % (B/A)	Peak Ht/DHBA Peak Ht,*
		Unextracted (A)	Extracted (B)		
DOPEG	5.7	0.69	0.58	84	1.29
NE	7.6	0.88	0.73	83	1.62
DHBA	17.7	0.58	0.45	78	1.00
DA	32.6	0.34	0.27	79	0.60

DOPEG, 3,4-dihydroxyphenylglycol; NE, norepinephrine; DHBA, 3,4-dihydroxybenzylamine; DA, dopamine. * ng extracted/ng.

RESULTS

Resting T_{co} was not altered by conditioning in the dose-response experiments but fell significantly in the HA group in the endogenous catecholamine studies (Table 2). Time to reach a T_{co} of 40.5°C during the HTT was unaffected by conditioning at 23°C but was significantly increased by conditioning at 35°C. Moreover, the time for T_{co} to rise from 39.5 to 40.5°C increased only 11% for the C groups but increased 54 and 77% for the HA groups (Table 2). T_{co} actually plateaued in some of the HA animals as shown previously (4).

Dose-Response Experiments

Before HA, the T_{co} decline (mean ± SE) in response to the 10-g dose of NE ranged from 0.6 to 1.8°C. Causes of this variation may include small variances in cannula placement, innate differences in sensitivity of the AH to NE, differences in functional capability of the vasodilatory mechanisms, or differences in other factors contributing to heat dissipation. To equalize the variations between groups, the animals were matched so that the mean T_{co} decline was 1.33 ± 0.09 and 1.32 ± 0.16 for C and HA groups, respectively. However, four HA and three C animals lost their implants during the conditioning sessions and had to be killed, leaving seven animals per group. These losses changed the mean T_{co} decrease in response to 10 μg NE to 1.50 ± 0.13°C for the C group and 0.96 ± 0.08°C for the HA group. After conditioning, there was no significant difference between the group responses to 10 μg NE (1.70 ± 0.10°C for the C and 1.80 ± 0.10°C for the HA). However, these values represented a 13% increase for the C group and an 88% increase for the HA group. Thus, to properly reflect the conditioning-induced changes, all postconditioning responses were normalized to the individual animals preconditioning response to 10 μg NE (Table 3).

Figure 1 shows the regression lines describing the linear portions of the dose-response curves between 2 and 20 μg NE. A split-plot analysis of variance showed that the slope of the regression line for the HA group

TABLE 2. *T_{co} response to heat-tolerance test, pre- and postconditioning*

Group	n		Resting T_{co}, °C	Time for T_{co} to Increase, min	
				To 40.5°C	From 39.5 to 40.5°C
Dose-response groups					
Control	7	Pre	38.5 ± 0.2	18.2 ± 2.5	9.1 ± 0.6
		Post	38.8 ± 0.1	19.9 ± 1.6	10.1 ± 1.3
Heat acclimated	7	Pre	38.4 ± 0.1	17.4 ± 1.1	7.9 ± 0.3
		Post	38.8 ± 0.1	21.8 ± 1.5*	12.2 ± 0.9*
Endogenous catecholamines groups					
Control	10	Pre	38.4 ± 0.2	17.2 ± 2.0	10.2 ± 1.4
		Post	38.0 ± 0.1	21.1 ± 1.4	11.3 ± 0.9
Heat acclimated	10	Pre	38.6 ± 0.1	18.8 ± 2.2	9.8 ± 1.5
		Post	38.2 ± 0.1*	30.1 ± 4.3*	17.3 ± 2.7*†

Values are means ± SE. T_{co}, core temperature. * $P < 0.05$, Pre- vs. postconditioning. † $P < 0.05$, Control vs. heat-acclimated group, postconditioning.

TABLE 3. *Postconditioning T_{co} decline following NE injections into AH*

NE Dose, μg	T_{co}, °C			
	Raw data		Normalized to 10 μg NE	
	Control	Heat acclimation	Control	Heat acclimation
2	0.8 ± 0.1	0.8 ± 0.1	0.5 ± 0.1	1.0 ± 0.3*
5	0.8 ± 0.2	1.2 ± 0.1	0.6 ± 0.1	1.4 ± 0.3
10	1.7 ± 0.1	1.8 ± 0.1	1.2 ± 0.1	1.9 ± 0.1*
20	2.3 ± 0.3	2.8 ± 0.2	1.6 ± 0.2	3.0 ± 0.2*
40	2.8 ± 0.3	2.6 ± 0.2	1.8 ± 0.2	2.9 ± 0.4

Values are means ± SE. T_{co}, core temperature; NE, norepinephrine; AH, anterior hypothalamus. * $P < 0.05$ vs. control groups.

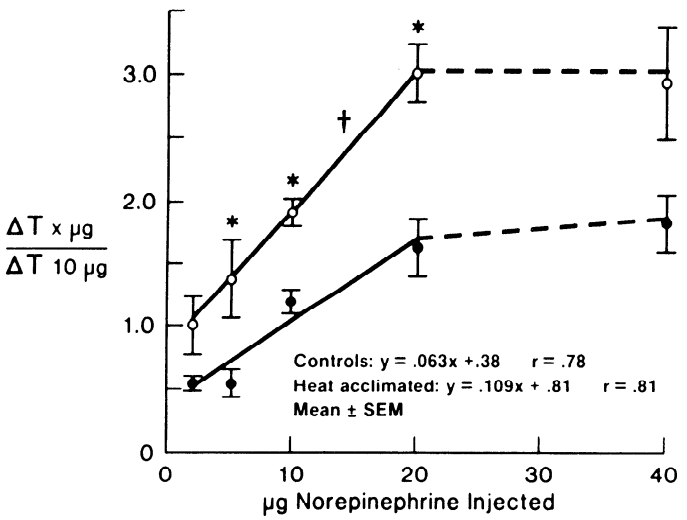

FIG. 1. Normalized colonic temperature response ($\Delta T \times \mu g / \Delta T$ 10 μg) to injections of norepinephrine into anterior hypothalamus of rat. * Significantly greater ($P < 0.05$) than control response at that dose. † Linear portion of dose-response curves significantly different ($P < 0.001$ split-plot analysis of variance).

was significantly greater than for the C group. Transformation of the response variable (ΔT) to $\log_{10}\Delta T$ normalized the slope difference, so that the curves could be treated as parallel lines. A test for the existence of a common additive factor in the response to each dose was then performed to determine if a parallel shift in the curve occurred. A highly significant difference ($P < 0.001$) was found. Thus exercise in the heat caused an increase in the slope as well as a shift to the left of the normalized regression line.

Endogenous Catecholamines

DOPEG values for the cerebellum and cortex were not calculated because interference between the large tissue homogenate peak and the relatively small trailing DOPEG peak during HPLC made accurate DOPEG determinations difficult. The smaller tissue samples for the PO and AH reduced the homogenate peak width and eliminated the interference.

Though there appeared to be a tendency for decreased concentrations in the exercise groups, the only significant differences in DA and NE content of the cerebellum and cortex was a decrease in cerebellar NE in the HA group vs. the S group (Table 4). Therefore, brain areas not generally recognized as participating in thermal control do not show general alteration (especially an increase) in catecholamine concentration as a result of HA.

TABLE 4. *Dopamine, norepinephrine, and DOPEG concentrations in brain areas*

Groups	*n*	Cerebellum	Cortex	Median Preoptic	Anterior Hypothalamus
		*Dopamine, ng/g tissue**			
Sedentary	6	18.4 ± 3.0	23.6 ± 3.4	255 ± 80	250 ± 50
Control	10	12.8 ± 1.0	23.2 ± 2.6	270 ± 40	240 ± 40
Heat acclimated	10	14.4 ± 1.8	24.6 ± 3.6	285 ± 50	215 ± 30
		Norepinephrine, ng/g tissue†			
Sedentary	6	222 ± 10	304 ± 36	1,650 ± 100	1,450 ± 200
Control	10	194 ± 22	242 ± 18	2,050 ± 150	1,850 ± 250
Heat acclimated	10	162 ± 16‡	238 ± 24	2,650 ± 400‡	2,250 ± 350
Kruskal-Wallis				0.05	0.23
Spearman				0.02	0.09
		DOPEG, ng/g tissue§			
Sedentary	6			300 ± 45	265 ± 45
Control	10			395 ± 35	365 ± 30
Heat acclimated	10			445 ± 45‡	395 ± 50
Kruskal-Wallis				0.10	0.14
Spearman				0.05	0.08

Values are means ± SE. Kruskal-Wallis and Spearman are probabilities of significant concentration trend in area. * Values reported to nearest 0.1 ng in cerebellum and cortex, to nearest 5 ng in PO and AH. † Values reported to nearest 1 ng in cerebellum and cortex, to nearest 50 ng in PO and AH. ‡ $P < 0.05$ vs. sedentary group (unpaired *t* test). § Values reported to nearest 5 ng.

In the PO and AH, DA concentrations showed no significant differences or apparent trends. NE and DOPEG were significantly increased only in the PO of HA animals compared with S animals. However, for both the PO and AH, NE and DOPEG mean values increased from S to C to HA groups. The Krusel-Wallis test showed this trend to be significant only in the PO for NE. The Spearman probabilities showed significance for NE and DOPEG in the PO and were below 0.10 for NE in both areas. These results suggest that increased NE storage in the brain areas where NE is involved as a neurotransmitter in the heat dissipation system occurs as the result of heat exposure during exercise.

DISCUSSION

The effects of heat acclimation in the present study were similar to our previous findings (4) and reflect the differences in T_{co} elevation in C and HA groups. The conditioning protocol used does not increase maximal O_2 consumption nor does it reduce resting or exercise heart rates (5), so improved performance in the heat is not due to increased cardiovascular capacity. The slight improvement in heat tolerance and responsiveness to centrally applied NE in the C group is attributed to the moderate rise in T_{co} in this group and is in accord with our previous findings (10). The significant decline in T_{co} following 9 wk of exercise in the heat in the endogenous catecholamine studies may have resulted from a decrease in basal metabolism. Because the heat exposure in the present

study was <1 h/day, it may be necessary to train in the heat >3 wk at this level of exposure to reduce T_{co} at rest.

Dose-Response Experiments

Statistical analysis of the regression lines describing the dose-response relationship constructed with normalized T_{co} data indicated that heat acclimation increased hypothalamic sensitivity as well as peripheral heat-dissipating capacity. The statistical analysis was based on the assumption that the system studied behaved according to classical drug-receptor theory (29). There are two major assumptions in this theory. *1*) The magnitude of the effect is directly proportional to the concentration of the drug-receptor complex, and *2*) the maximal effect occurs when all receptors are occupied. In this study, the injection of NE into the AH resulted in peripheral vasodilation, which caused heat loss and thus reduced T_{co}. Because of the intervening steps between NE-receptor interaction and the decline in T_{co}, the dose-response relationship may not exactly reflect the events caused by the formation of the drug-receptor complex. Thus it cannot be asserted that the system met the two assumptions of classical drug-receptor theory. Although the system appeared to behave proportionally to give a maximal response when all receptors were occupied, the data did not fit a hyperbola when dose and response were plotted on linear scales and they did not fit a Lineweaver-Burk (double reciprocal) plot in a linear fashion. Moreover, within the range of standard errors, the response of the HA group appears to be a constant multiple of the C group response. When the C group responses shown in Table 3 were multiplied by 2.9/1.8 (ratio of HA to C group response to 40 μg NE) to equalize the maximal response of both groups, the values were not statistically different within doses. Peripheral adaptation, such as a set percentage increase in response to a given central output without any alteration in that central output, could account for such a uniform increase in response to all doses. Thus, despite the statistical analysis performed, it must be concluded that heat acclimation increases NE-induced peripheral heat-dissipating capacity. However, these data do not rule out a central change in receptor sensitivity.

Endogenous Catecholamines

The standard error for NE in both the PO and AH grew progressively larger from S to C to HA groups (Table 4). This trend is logical considering that inter-animal differences exist in exercise and heat responses. Thus C animals would have variation due to different exercise responses superimposed on the normal interanimal variation, and HA animals would have a further added variation due to different heat stress responses. To eliminate further variations due to different exercise and heat tolerance capacities, endogenous catecholamines were measured 24 h after the last exercise period and at rest.

The apparent parallel increases in NE and DOPEG in the PO and AH indicate that both areas are stressed similarly by exercise and heat exposure. The significantly increased NE and DOPEG in HA rats vs. S rats, the trend of increasing NE and DOPEG in the PO, and the closeness of the other values to attaining significance (despite the relatively small sample size) indicate that increased catecholamine storage is probably a facet of central adaptation during heat acclimation. It is believed that DOPEG is an intracelllar presynaptic metabolite of NE in the rat (25), so it would be in equilibrium with endogenous NE stores. Thus parallelism between the increases in NE and DOPEG in the PO and AH would be expected if changes in NE had occurred. The fact that parallel increases were seen suggests that the observed values were real changes rather than random variation. Whether the higher NE and DOPEG levels in the PO have any functional significance is unknown.

The NE concentration in the cerebellum and cortex showed a trend toward a decrease in the C and HA animals, which was significant for the HA vs. S animals in the cerebellum. Conversely, the trend was toward an increase in NE in the PO and AH of C and HA animals, which was significant for the HA vs. S animals in the PO. These differences may reflect the role of each brain part during exercise. Acute stress produces intense general activation of noradrenergic neurons (30). Each brain region responds differently to a particular stress with its own rate of NE release (24). Synthesis of NE in a particular area may be unable to match release and catabolism, so NE concentration in that area would be temporarily reduced (19). The magnitude of the final depletion is dependent on the functional pool size of NE (13). Recovery rates vary among brain areas depending on the persistence of local neuronal activity (28). Conversely, operant behavior enhances catecholamine synthesis in different areas of the rat brain in different degrees (15) so that the increased release that also occurs under these conditions does not result in a decreased catecholamine concentration. Thus the stress of the exercise and heat of this study may have affected the cortex and cerebellum in a manner to reduce the NE level 24 h after exercise, whereas the overall effect on the heat dissipation pathways in the PO and AH was to increase total NE.

At rest at an ambient temperature of 23°C, injection of the α-adrenergic receptor blocker phentolamine into the rat AH does not affect resting T_{co}. Thus hypothalamic noradrenergic heat dissipation neurons are not active under these conditions (11). Because the animals in the endogenous catecholamines experiment were killed at 23°C, the greater concentration of NE in the PO and AH therefore implies a presynaptic increase in NE storage. Conversely, noradrenergic inactivity at 23°C means that NE injected into the AH acted postsynaptically to induce the T_{co} drop. Thus our results indicate that both presynaptic and postsynaptic adaptations can be induced in the CNS by recurrent exposure to a natural external stress.

One might surmise that other adaptations would occur concurrently with those measured here. In the AH, presynaptic changes could include any or all aspects of NE synthesis and storage. Indeed, Braganza and Wilson (3)

have demonstrated a reduction in brain NE turnover in male Japanese quail following passive heat acclimation. Rates of release and reuptake of NE in response to a given stress or in response to maximal stress could also be altered, especially since peripheral heat-dissipating capacity is increased by heat acclimation. The dose-response data indicate a possible increase in postsynaptic sensitivity to NE, perhaps through alteration of NE interaction with the α-adrenergic receptors and/or other neurological events distal to the hypothalamic noradrenergic synapse.

In addition to the adaptations of the heat dissipation system suggested above, changes within the temperature-sensing and body temperature-regulating centers might also occur. Fluctuations in firing rates and thermosensitivity of warm-sensitive neurons of the PO and AH occur even when central and peripheral temperatures are constant (2). Independence of firing rates from peripheral inputs is further demonstrated by fluctuations within in vitro hypothalamic tissue slices (17). Given this apparent natural variation in activity of temperature-sensitive neurons with the thermoregulatory control areas, the ability to achieve a permanent shift in rate with chronic heat exposure is easily conceivable. Future experimentation could readily test these possibilities.

The authors acknowledge the secretarial expertise of Joan Seye.

This research was supported by Office of Naval Research Contract N-00014-75-C-0597.

Received 31 August 1983; accepted in final form 16 January 1985.

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