



Chronic Heat Stress-Induced Alterations in Hormonal Profile (Corticosterone, T3, T4, TSH) and Oxidative Stress Markers (MDA, GSH, GPx) in Laboratory Rats

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Abstract: Chronic heat stress disrupts neuroendocrine balance and promotes oxidative damage, yet the duration-dependence of simultaneous hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-thyroid (HPT) axis responses and antioxidant status remains poorly defined. This study quantified the effects of daily heat exposure (2, 4, or 8 h/day at 42°C for 21 days) on serum corticosterone, triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH), and on hepatic oxidative markers malondialdehyde (MDA), reduced glutathione (GSH), and glutathione peroxidase (GPx) in adult male Wistar rats. Thirty-two rats (180–220 g) were randomized into four groups (n = 8): control and three heat-stressed groups (HS-2, HS-4, HS-8). ELISA quantified hormones, and oxidative markers were measured spectrophotometrically; data were analyzed by one-way ANOVA with Tukey HSD and Pearson correlation. Heat stress produced duration-dependent endocrine and oxidative changes ($p < 0.001$). Corticosterone rose 3.5-fold, from 45.2 ± 4.1 to 158.7 ± 13.2 ng/mL in HS-8, whereas T3, T4, and TSH fell by 48%, 55%, and 57%, respectively. MDA increased 3.7-fold (2.14 ± 0.18 to 7.88 ± 0.61 nmol/mL), and GSH and GPx declined by 66% and 71%. Corticosterone correlated positively with MDA ($r = +0.892$) and negatively with GSH ($r = -0.874$); T3 correlated negatively with MDA ($r = -0.861$) and T4 positively with GPx ($r = +0.847$). Chronic heat stress, therefore, causes duration-dependent HPA-axis activation, HPT-axis suppression, and antioxidant depletion, and the tight hormone-redox coupling supports the use of combined hormonal-antioxidant biomarker panels for grading heat-stress severity.

Keywords: Heat stress; corticosterone; thyroid hormones; malondialdehyde; glutathione peroxidase

1. Introduction

Heat stress arises when thermal load exceeds thermoregulatory capacity, activating coordinated neuroendocrine, metabolic, and molecular responses to restore homeostasis [1]. As climate warming intensifies the incidence of extreme-temperature episodes, the physiological consequences of heat exposure have become a central biomedical concern [2]. The hypothalamic-pituitary-adrenal (HPA) axis the central stress-regulating mechanism: rising temperature drives hypothalamic CRH release, pituitary ACTH secretion, and adrenal glucocorticoid output, with corticosterone the dominant rodent glucocorticoid and a quantitative index of HPA activation [3]. Sustained corticosterone

elevation promotes immunosuppression, metabolic dysregulation, infertility, and oxidative injury [4].

In parallel, prolonged stress inhibits the hypothalamic-pituitary-thyroid (HPT) axis by reducing TRH, TSH, and, consequently, T3 and T4 a paradoxical but adaptive reduction in thermogenic drive [5]. Heat is also associated with oxidative stress since high temperatures result in increased electron leakage and superoxide formation but decrease the activities of antioxidant enzymes [6]; this affects the reactive oxygen species to antioxidant ratio [7]. Increased levels of MDA are indicative of lipid peroxidation in cell membranes whereas GSH and GPx values are used to indicate non-enzymatic and enzymatic antioxidants respectively; similar levels of antioxidant depletion, i.e. high MDA and low GSH and GPx levels, were noted in other stress models involving rodents, such as streptozotocin-induced diabetes [8], aspirin-induced gastric damage [9], hyperhomocysteinemia [10] and aging induced by d-galactose [11].

Despite the individual characterization of the heat-induced changes in the hormonal and oxidative systems, limited research has explored the impact of heat on HPA axis, HPT axis, and oxidative status concomitantly in different durations of heat exposure in a single experimental model [12,13]. Thus, this research aimed to evaluate the heat-induced changes in the serum hormones (corticosterone, T3, T4, and TSH) and hepatic oxidative markers (MDA, GSH, and GPx) following the different durations of heat exposure in adult male Wistar rats for 21 days.

2. Materials and Methods

2.1 Ethical approval

All experiments were conducted based on NIH protocols for animal handling and care and given clearance from the Institutional Animal Ethics Committee. The minimum number of animals was used, and they suffered minimal pain.

2.2 Animals and housing

Adult male Wistar rats (10–12 weeks, 180–220 g) were housed individually in stainless-steel cages (48 × 27 × 20 cm) at $22 \pm 1^\circ\text{C}$, $50 \pm 5\%$ relative humidity, and a 12 h light/dark cycle (lights on at 07:00 h). Standard diet (20% protein, 5% fat, 60% carbohydrates, trace minerals) and tap water were freely accessible throughout the experiment.

2.3 Experimental design and heat-stress protocol

Once a 7-day acclimatization period had elapsed, thirty-two rats were distributed randomly into four groups of eight using a computer-generated randomization technique (Table 1). Heat stress was introduced into a thermostatically controlled box at $42 \pm 0.5^\circ\text{C}$ and $40 \pm 5\%$ relative humidity during the light phase from 09:00 hours on a daily basis, while controls were kept at $22 \pm 1^\circ\text{C}$ for similar periods. Body temperatures were measured rectally ($\pm 0.1^\circ\text{C}$) before and after each experiment. The 21-day protocol used is based on a well-established model of chronic heat stress [14].

Table 1. Groups in Experiment, Treatments and Housing Condition.

Group	n	Treatment	Housing conditions
I (Control)	8	Standard conditions; no heat exposure	$22 \pm 1^\circ\text{C}$, 12 h light/dark
II (HS-2)	8	Heat stress: 2 h/day, 42°C , 21 days	42°C during exposure; $22 \pm 1^\circ\text{C}$ at rest
III (HS-4)	8	Heat stress: 4 h/day, 42°C , 21 days	42°C during exposure; $22 \pm 1^\circ\text{C}$ at rest
IV (HS-8)	8	Heat stress: 8 h/day, 42°C , 21 days	42°C during exposure; $22 \pm 1^\circ\text{C}$ at rest

n = animals per group; HS = heat stress. All animals received food and water ad libitum throughout the experiment.

2.4 Sample collection

On day 22, after 18 h following the last treatment, The rats were anesthetized using sodium pentobarbital (60 mg/kg, i.p.). Anesthesia was induced 18 h post-treatment to circumvent the occurrence of any acutely elevated levels of corticosterone (with half-life ≈ 60 –70 min in rats). The 18-h period was chosen to measure chronic changes in HPA activity rather than acute stress-induced changes, thus the high corticosterone levels measured represent a chronic change in neuroendocrine set point rather than a stress-induced acute increase. Blood was collected through heart puncture. Serum was collected by centrifugation

(3000 × g, 15 min, 4°C) and stored at −80°C. Liver tissue was harvested, washed with cold PBS (pH 7.4), frozen in liquid nitrogen and stored at −80°C.

2.5 Hormonal assays

Serum corticosterone concentrations were determined using competitive ELISA kits (DetectX, Arbor Assays, Ann Arbor, MI, USA; intra/inter-assay CV < 8%/12%), while T3, T4, and TSH were quantified using sandwich ELISA kits (BioAssay Systems, Hayward, CA, USA), cross-validated to measure rat serum (limit of detection: 0.5 ng/dL, 0.1 µg/dL, and 0.02 µIU/mL, respectively).

2.6 Oxidative stress markers

The liver was homogenized at 10% (w/v) in cold PBS (pH 7.4) and centrifuged at 10,000 × g for 15 min at 4°C. MDA level was evaluated using the TBARS assay [15] (95°C, 60 min; 532 nm; tetraethoxypropane as standard). GSH level was assessed by the Ellman DTNB assay [16] (412 nm), and GPx activity by NADPH oxidation at 340 nm [17]. Total protein concentration was estimated by Bradford method (BSA as standard) to ensure

2.7 Statistical analysis

Values are expressed as mean ± SD (SPSS 26.0, IBM, Armonk, NY, USA). Normality was validated using the Shapiro-Wilk test. One-way ANOVA with Tukey's honestly significant difference test and Pearson correlation were used to compare groups and hormones with redox status. Significance was set at $p < 0.05$, with $p < 0.01$ and $p < 0.001$ reported where applicable. The sample size of $n = 8$ per group was based on published chronic heat-stress rodent models [12,13] and is acknowledged as a study limitation given the multiplicity of correlated endpoints (four hormonal and three oxidative markers) assessed simultaneously.

3. Results and Discussion

3.1. Body weight and core temperature

No mortality occurred. Heat-stressed rats appeared to gain less weight than controls, consistent with reduced intake and higher energy expenditure. Quantitative body weight and food-intake data were not formally recorded in this study; this represents a limitation, as caloric restriction can independently suppress HPT axis activity and elevate corticosterone, and the contribution of reduced food intake to the hormonal changes observed cannot be fully excluded. Rectal temperature increased with exposure duration: 38.8 ± 0.4 , 39.4 ± 0.5 , and $40.1 \pm 0.6^\circ\text{C}$ in HS-2, HS-4, and HS-8 versus $36.9 \pm 0.3^\circ\text{C}$ in controls (all $p < 0.001$), confirming graded thermal load.

3.2. Hormonal responses

Corticosterone increased dose-dependently to 1.7-, 2.5-, and 3.5-fold of control in HS-2, HS-4, and HS-8 ($45.2 \pm 4.1 \rightarrow 158.7 \pm 13.2$ ng/mL; $p < 0.001$) (Table 2, Figure 1A). Contrastingly, in HS-8, T3 fell 48% ($92.4 \pm 7.2 \rightarrow 47.8 \pm 3.5$ ng/dL), T4 fell 55% ($5.8 \pm 0.4 \rightarrow 2.6 \pm 0.2$ µg/dL), and TSH fell 57% ($1.42 \pm 0.11 \rightarrow 0.61 \pm 0.05$ µIU/mL) (all $p < 0.001$). These opposing trajectories are illustrated in Figure 1, which contrasts the dose-dependent rise in corticosterone (Figure 1A) with the progressive, duration-dependent suppression of T3 (Figure 1B), T4 (Figure 1C), and TSH (Figure 1D) across the control, HS-2, HS-4, and HS-8 groups. The concurrent decline in TSH and thyroid hormones indicates central HPT suppression rather than primary hypothyroidism. The rise in corticosterone reflects HPA activation via thermosensory drive of paraventricular CRH neurons [18], while the magnitude in HS-8 suggests impaired glucocorticoid negative feedback typical of chronic stress [19]. Such hypercorticosteronemia underlies catabolism, immunosuppression, and circadian disruption [20]. Glucocorticoids suppress TRH transcription via glucocorticoid-response elements in the TRH promoter and inhibit pituitary thyrotrophs [5, 21], consistent with the strong inverse corticosterone-thyroid correlations below and recent evidence of crosstalk [22]. Reduced thyroid output may additionally be adaptive, lowering uncoupled oxidative phosphorylation and thermogenesis [23].

Table 2. Serum hormonal concentrations across experimental groups (mean $\pm$ SD, n = 8).

Parameter	Control (I)	HS-2 (II)	HS-4 (III)	HS-8 (IV)
Corticosterone (ng/mL)	45.2 $\pm$ 4.1	78.6 $\pm$ 6.3*	112.4 $\pm$ 9.8**	158.7 $\pm$ 13.2***
T3 (ng/dL)	92.4 $\pm$ 7.2	78.1 $\pm$ 5.9*	61.3 $\pm$ 4.7**	47.8 $\pm$ 3.5***
T4 (μ g/dL)	5.8 $\pm$ 0.4	4.9 $\pm$ 0.3*	3.7 $\pm$ 0.3**	2.6 $\pm$ 0.2***
TSH (μ IU/mL)	1.42 $\pm$ 0.11	1.18 $\pm$ 0.09*	0.87 $\pm$ 0.07**	0.61 $\pm$ 0.05***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. Control (Tukey HSD). T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

3.3 Oxidative stress markers

MDA rose to 3.7-fold of control ($2.14 \pm 0.18 \rightarrow 7.88 \pm 0.61$ nmol/mL) while GSH and GPx fell 66% ($28.4 \pm 2.1 \rightarrow 9.7 \pm 0.9$ μ mol/L) and 71% ($18.6 \pm 1.4 \rightarrow 5.4 \pm 0.5$ U/mL), respectively, in HS-8 (all $p < 0.001$) (Table 3, Figure 2A–C). Figure 2 illustrates the oxidation status deterioration depending on time, as evidenced by the increasing hepatic MDA concentration in the control group relative to the HS-2, HS-4, and HS-8 group (Figure 2A), accompanied by the decreasing levels of GSH (Figure 2B) and GPx (Figure 2C). This effect agrees with meta-analytical data obtained from studies in heat-stressed animals [24] and suggests the mitochondrial dysfunction associated with increased electron leakage and generation of ROS [25]. Moreover, heat stimulation activates phospholipase A₂ that releases arachidonic acid and triggers lipid peroxidation process [26]; since GSH depletion affects the GPx hydroperoxide scavenging activity, a vicious circle is formed [27]. The decreasing GPx activity may be explained by a variety of reasons: (i) decreased substrate availability because of the faster GSH consumption relative to its generation through glutathione reductase/NADPH pathway; (ii) GPx enzyme inactivation due to the oxidative attack of selenocysteine residues in the active center caused by the excess ROS production; and (iii) possibly transcriptional inhibition of GPx1 and GPx4 genes due to glucocorticoids.

Table 3. Oxidative stress markers across experimental groups (mean $\pm$ SD, n = 8).

Parameter	Control (I)	HS-2 (II)	HS-4 (III)	HS-8 (IV)
MDA (nmol/mL)	2.14 $\pm$ 0.18	3.72 $\pm$ 0.29*	5.61 $\pm$ 0.42**	7.88 $\pm$ 0.61***
GSH (μ mol/L)	28.4 $\pm$ 2.1	22.1 $\pm$ 1.8*	15.3 $\pm$ 1.3**	9.7 $\pm$ 0.9***
GPx (U/mL)	18.6 $\pm$ 1.4	14.2 $\pm$ 1.1*	9.8 $\pm$ 0.8**	5.4 $\pm$ 0.5***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. Control (Tukey HSD). MDA = malondialdehyde; GSH = reduced glutathione; GPx = glutathione peroxidase.

3.4 Hormone-redox correlations

Corticosterone correlated positively with MDA ($r = +0.892$) and inversely correlated with GSH ($r = -0.874$); T3 correlated negatively with MDA ($r = -0.861$), T4 positively with GPx ($r = +0.847$), and TSH positively with GSH ($r = +0.823$) (all $p < 0.001$) (Table 4, Figure 2D). The above Pearson correlations were calculated on all 32 individuals obtained from all four groups. The reason why there is an inherent strength to these correlations is due to the fact that there are differences in systematic design in the groups (graded heat duration). These correlations should thus be seen as a reflection of variance between the groups due to the effects of the treatment rather than biological coupling. They should not be taken as evidence of a biochemical association. Partial correlations taking into account the effect of group should be done in further research. The corticosterone-MDA coupling agrees with glucocorticoid pro-oxidant actions via Nrf2 down-regulation and mitochondrial ROS [28], whereas thyroid-antioxidant links reflect thyroid-hormone transcriptional control of GPx and related enzymes [29]; transcriptomic studies report concordant heat-responsive gene networks [14]. It should also be acknowledged that oxidative stress was assessed in hepatic tissue, which was chosen for practical reasons of yield and technical reproducibility. The liver is a metabolically central organ and a valid index of systemic redox status; however, oxidative stress in the adrenal cortex, hypothalamus, or anterior pituitary would be more directly mechanistically informative for HPA/HPT-axis conclusions and represents

an important direction for future work. Collectively, corticosterone, T3, T4, and MDA form a coherent biomarker panel for grading heat-stress severity, relevant to occupational and tropical exposures.

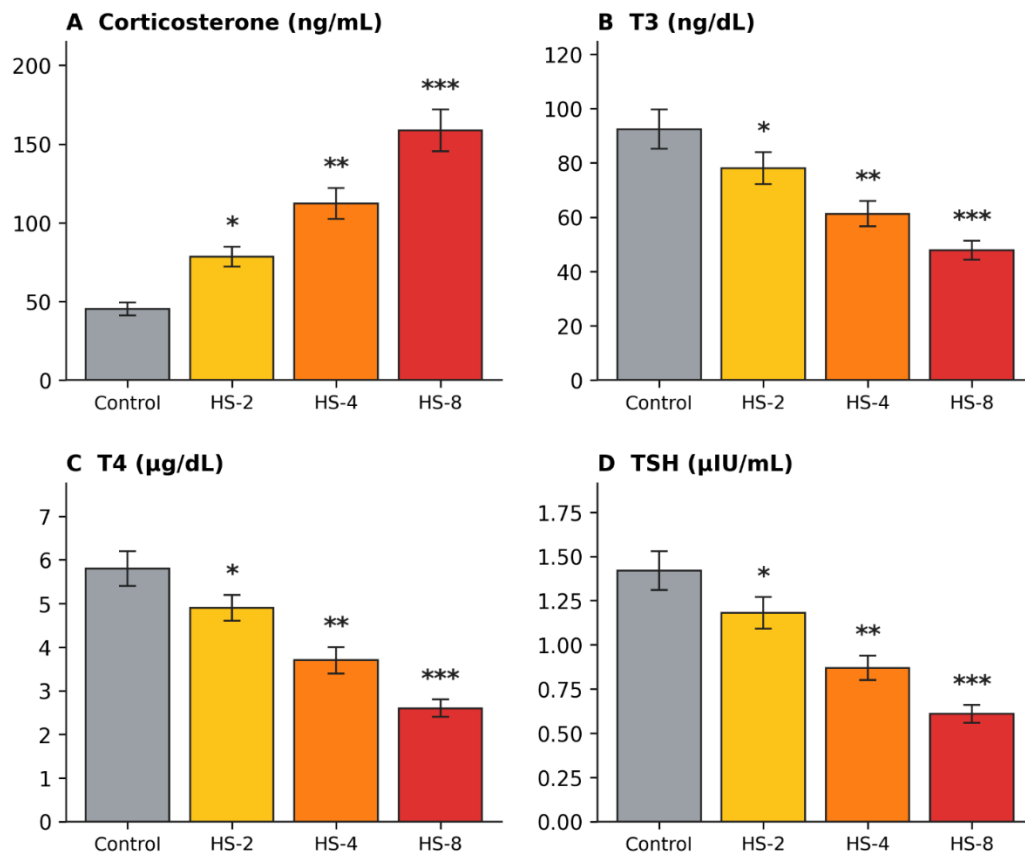


Figure 1. Duration-dependent effects of chronic heat stress (42 °C, 21 days) on serum hormones in adult male Wistar rats. Serum (A) corticosterone, (B) triiodothyronine (T3), (C) thyroxine (T4), and (D) thyroid-stimulating hormone (TSH) in control and heat-stressed groups exposed for 2 (HS-2), 4 (HS-4), or 8 h/day (HS-8). Bars are mean $\pm$ SD ($n = 8$). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ against control (one-way ANOVA, Tukey HSD). Corticosterone rose dose-dependently to 3.5-fold of control, whereas T3, T4, and TSH fell by 48%, 55%, and 57%, indicating concurrent HPA-axis activation and HPT-axis suppression.

Table 4. Pearson correlation coefficients between hormonal and oxidative stress markers.

Variable pair	Pearson r	p-value	Interpretation
Corticosterone vs MDA	+0.892	< 0.001	Strong positive
Corticosterone vs GSH	−0.874	< 0.001	Strong negative
T3 vs MDA	−0.861	< 0.001	Strong negative
T4 vs GPx	+0.847	< 0.001	Strong positive
TSH vs GSH	+0.823	< 0.001	Strong positive

All correlations are significant at $p < 0.001$. r = Pearson correlation coefficient.

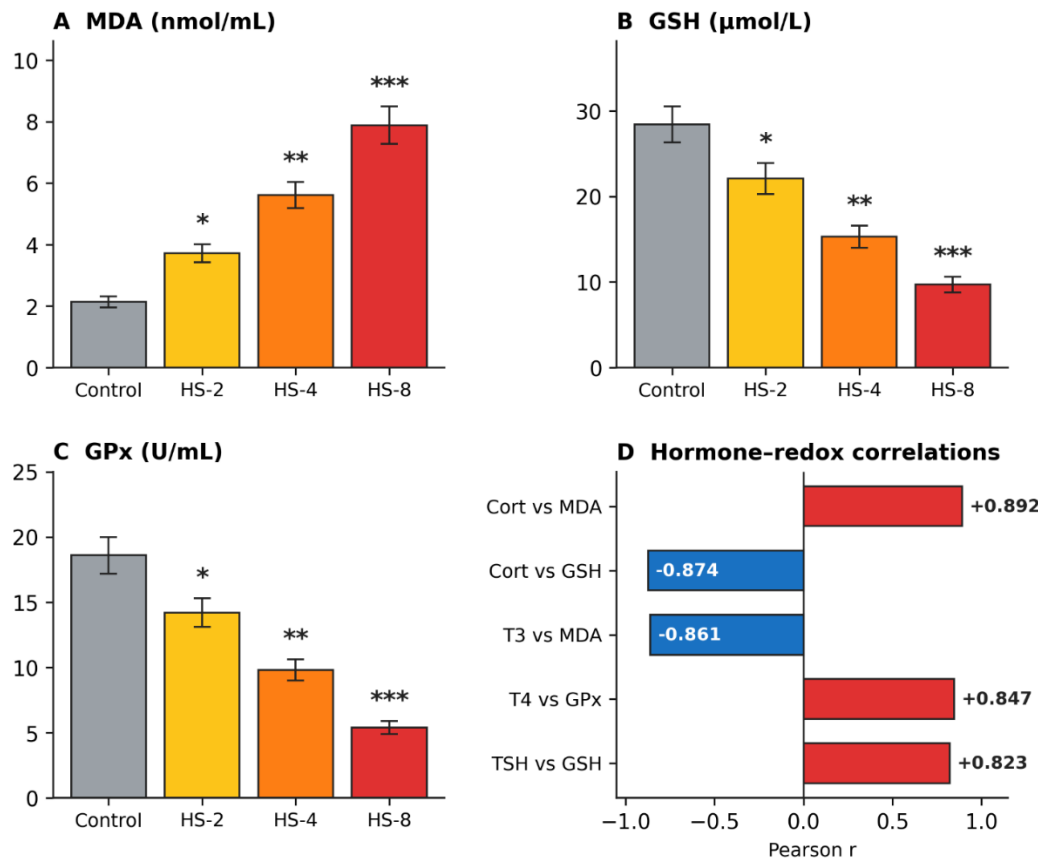


Figure 2. Duration-dependent oxidative stress and hormone-redox associations. Hepatic (A) malondialdehyde (MDA), (B) reduced glutathione (GSH), and (C) glutathione peroxidase (GPx) across control and heat-stressed groups (mean $\pm$ SD, $n = 8$; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus control, one-way ANOVA with Tukey HSD). (D) Pearson correlation coefficients between hormonal and oxidative markers (all $p < 0.001$); red and blue denote positive and negative associations, respectively. MDA increased 3.7-fold while GSH and GPx declined 66% and 71%; corticosterone correlated positively with MDA ($r = +0.892$) and negatively with GSH ($r = -0.874$).

3.5 Limitations

Male rats only were investigated, along with one temperature (42°C), thus ignoring any sex-related effects as well as temperature-humidity combination effects; oxidative stress was assessed in the liver and not in neuroendocrine tissues; and there is yet to be a molecular characterization of the suppression of antioxidants by glucocorticoids based on the results of transcriptomic and proteomic analyses. Concerning the temperature used, 42°C is an extremely high temperature not only because it is outside the physiological range but also because it is used to assess heat stress of laboratory housed rats; real-life heat stress of livestock and humans occurs at much lower temperatures ranging from 35–38°C with high humidity levels. As far as the sex of the animal is concerned, the restriction to males only is not a trivial limitation since estrogens regulate not only HPA reactivity but also the activity of antioxidant enzymes including GPx and GSH synthetic enzymes.

4. Conclusions

Chronic 42°C exposure for 21 days produced duration-dependent HPA activation (corticosterone rose to 3.5-fold of control at 8 h/day) and HPT suppression (T3, T4, and TSH down 48–57%) alongside progressive oxidative stress (MDA rose to 3.7-fold of control; GSH –66%; GPx –71%) in adult male Wistar rats. The strong hormone-redox correlations indicate integrated endocrine-oxidative mechanisms in heat-stress pathophysiology and support the use of combined hormonal-antioxidant biomarker panels to assess heat-stress severity. As extreme-heat events grow more frequent, such combined biomarker signatures could aid

risk stratification in occupational, clinical, and livestock contexts. Future work should incorporate both sexes, realistic temperature-humidity profiles, neuroendocrine-tissue redox assessment, and molecular pathway analysis.

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