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RECEIVED 28 August 2025

ACCEPTED 08 October 2025

PUBLISHED 28 October 2025

CITATION

Serrano-Jara D, Agea I, Romero G,
Argente MJ, Santacreu MA and García MdL
(2025) Genetic correlated responses to
selection for resilience in key inflammatory
and stress biomarkers under heat
stress of rabbits.
Front. Anim. Sci. 6:1694508.
doi: 10.3389/fanim.2025.1694508

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Genetic correlated responses to selection for resilience in key inflammatory and stress biomarkers under heat stress of rabbits

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Heat stress is a major challenge for rabbit production, due to the species' limited thermoregulatory capacity. Two rabbit lines were divergently selected over 17 generations for environmental variance in litter size: the Low line, with greater resilience, and the High line, with less resilience. This study aimed to compare acute stress and inflammatory responses in males from both lines under heat stress (temperature–humidity index, THI ≥ 27.8) and thermoneutral (THI < 27.8) conditions. Forty males (20 per line) were evaluated for eyeball temperature via infra-red thermography before and after a semen collection stressor, and for plasma cortisol, C-reactive protein (CRP), and tumor necrosis factor- α (TNF- α) by ELISA. Bayesian methodology was used for statistical analysis. The Low line maintained lower eyeball temperatures than the High line under both thermal conditions ($P > 90\%$), while retaining normal acute stress responses. Under heat stress, the Low line also showed lower TNF- α levels, and under both conditions, lower cortisol levels ($P > 90\%$). CRP did not differ between lines or thermal conditions ($P < 90\%$). These results indicate that selection for reduced litter size variability improves thermal regulation and attenuates stress-associated physiological responses, supporting its use to enhance resilience, welfare, and sustainability in rabbit production.

KEYWORDS

resilience, heat stress, infra-red thermography, litter size variability, stress biomarkers, CRP, TNF- α , cortisol

1 Introduction

The global rise in temperatures due to climate change is a challenge for livestock production. The Mediterranean region constitutes a hottest and large area of highly specialized and technically skilled rabbit production (Giorgi and Lionello, 2008; Cullere and Dalle-Zotte, 2018). Heat stress is one of the main factors directly and indirectly linked to environmental stress in rabbits (Oladimeji et al., 2022; Ebeid et al., 2023).

Rabbits are homeothermic animals that are very sensitive to high temperatures (Marai et al., 2002). Due to their thick fur and the absence of sweat glands, this species has a low thermoregulatory capacity (Marai et al., 2001; Yağci et al., 2006). The zone of thermoneutrality in rabbits is between 15 to 25 °C and 55–65% of humidity, the critical temperature from 27 to 30 °C, and 35 °C is the maximum temperature above which rabbits cannot regulate their body temperature (Marai et al., 2001; Cervera and Carmona, 2010; Nielsen et al., 2022; Oladimeji et al., 2022). Heat stress occurs when rabbits are unable to maintain equilibrium between the heat they produce and the heat they lose.

Heat stress negatively impacts average daily gain and feed conversion ratio (Jaén-Téllez et al., 2021; Liang et al., 2022), while also impairing reproductive performance. This includes reduced sperm quality in males (Pei et al., 2012; Huang et al., 2023) and decreased fertility, embryo implantation rates, embryo quality and birth weights in females (García and Argente, 2017; Liang et al., 2022; Ebeid et al., 2023). It also reduces the quality of the processed product (Zeferino et al., 2013) and increases the mortality rate (Yan and Li, 2008).

High ambient temperatures activate the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic adrenomedullary system, leading to increased plasma levels of cortisol and catecholamines, and body temperature (Hennessy, 1997; Möstl and Palme 2002). Infrared thermography (IRT) enables the detection of variations in body temperature (Agea et al., 2021; Jaén-Téllez et al., 2021), which serves as an indicator of heat stress and is less invasive than measuring plasma cortisol levels. In particular, the rabbit's eyeball provides an optimal anatomical site for rapidly assessing the response to acute stress stimuli (Serrano-Jara et al., 2025).

Acute stress dysregulates the immune system, increasing susceptibility to diseases (Mormede et al., 2018). This homeostatic disruption, caused by factors like infections, tissue damage, or stress itself, triggers an acute phase response (Kushner, 1988). In turn, the acute phase response induces the release of cytokines, which alter the plasma concentration of acute phase proteins (Eckersall and Bell, 2010). Among these, TNF- α , a pro-inflammatory cytokine, and C-reactive protein (CRP), a positive acute phase protein, are widely used as biomarkers for assessing stress and animal welfare (Gutiérrez et al., 2009; Argente et al., 2019; Beloumi et al., 2020).

TNF- α is a central mediator in multiple physiological and disease-related processes. In humans, it contributes to inflammation by activating neutrophils and disrupting intestinal absorption (Deem et al., 1991; Suter et al., 1992). Studies in rodents

have linked TNF- α to oxidative stress-induced cell damage in mice and regulation of the HPA axis in rats (Bohlinger et al., 1996; Takao et al., 1997). In rabbits, evidence suggests it impairs jejunal absorption of nutrients such as L-leucine and D-fructose (Abad et al., 2002; García-Herrera et al., 2004). CRP is synthesized in the liver and its serum concentrations increase in response to an inflammatory process. In rabbits, plasma CRP levels have been associated with reproductive, dental, and musculoskeletal diseases (Oohashi et al., 2019). In goats, it has been linked to metritis and mastitis, and in sows to infectious processes and stress situations (Saco and Bassols, 2022).

Resilience is the capacity of the animal to be minimally affected by a disturbance or to rapidly return to the physiological, behavioral, cognitive, health, affective and production states that pertained before exposure to a disturbance (Colditz and Hine, 2016). A divergent selection program was developed in rabbits with the aim of improving resilience. However, resilience is a trait that is difficult to measure directly. For this reason, the team proposed assessing it through the environmental variance in litter size within females. The Low line, which developed greater resilience as a result of the selection process, was selected for reduced litter size variability, whereas the High line, with comparatively less resilience, was selected for increased variability (Blasco et al., 2017).

The genetic program proved successful: after 12 generations of selection, litter size variability was 2.5 kits² in the Low line and 5.5 kits² in the High line. Females from the Low line showed a lower inflammatory response to infectious challenges and greater disease resistance compared to those from the High line. This was reflected in lower female mortality at parturition, reduced litter mortality at birth and weaning, and greater uniformity in litter weight at weaning (Argente et al., 2017). Moreover, females from the High line exhibited higher stress responses, lower disease resistance, and smaller litter sizes than those from the Low line (Argente et al., 2017, 2019; Beloumi et al., 2020), confirming that the Low line is the more resilient than the High line.

The study aims to assess the acute stress and inflammatory correlated response in two divergent selected rabbit lines for litter size variability, under both with and without environmental heat stress, by monitoring body temperature and plasma levels of CRP, TNF- α , and cortisol.

2 Material and methods

The experimental procedures with animals were approved by the General Directorate of Agriculture, Livestock and Fisheries of the Generalitat Valenciana with code 2022/VSC/PEA/0226.

2.1 Animals and experimental design

The research was carried out on the farm at Miguel Hernandez University in Orihuela (38.06747347849708, -0.9821394614708082),

Alicante (Spain). The facilities included equipped with forced ventilation and cooling, and a photoperiod of 16 hours of light and 8 hours of darkness. Animals were housed in individual cages, fed with a commercial diet (16.1% of crude protein; 3.522 kcal/kg of digestible energy) and provided water ad libitum.

In the selection process for environmental variability of litter size, each line includes approximately 125 ± 5 females and 25 males per generation. Selection is based on the phenotypic variance of litter size within each female, after correcting litter size for year-season effects and parity-lactation status. Once systematic effects are corrected, the intra-doe phenotypic variance reflects environmental variability. The selection intensity for each generation is 30%. To reduce inbreeding, each male is mated with five females, and one male offspring from the best female is selected to breed the next generation (see more details in [Blasco et al., 2017](#)). Each generation lasts 12 months.

A total of 40 males, 20 each from the 17th generation of the High (heterogeneous) and Low (homogeneous) lines, were used in this study. The age range was between 5 and 10 months on both lines. The average weight was 3.53 kg.

From ambient temperature and relative humidity, the temperature/humidity index (THI) was calculated: $THI = t - [(0.31 - 0.31 \times rh) \times (t - 14.4)]$ where t = average temperature of the farm from the time of infra-red imaging until 24 hours before and rh = relative humidity/100, collected in the same way as temperature ([Marai et al., 2001](#)). The weeks in which data were collected were classified according to the THI into heat stressed ($THI \geq 27.8$) and non-heat stressed ($THI < 27.8$) ([Marai et al., 2001](#)). According to the THI, the groups were classified into High Stressed Line (HS), High Non-Stressed Line (HNS), Low Stressed Line (LS) and Low Non-Stressed Line (LNS).

2.2 Temperature records

A total of 120 body temperature records were taken from the High and Low lines (60 per line; 30 per group). Body temperature emissivity was measured using IRT on the eyeball. The images were obtained using a [®]FLIR SC660 thermal imaging camera and were processed with the [®]ThermaCAM Researcher Pro 2.10 software to obtain the temperature record. The camera was calibrated according to temperature, relative humidity, emissivity (98%), and distance from the subject (0.7 m).

Data collection was carried out for 12 weeks, between June 2023 and February 2024. Body temperature measurements at the eyeball were taken at three moments: minute 0 (corresponding to basal temperature), minute 1 (one minute after the application of the acute stressor), and minute 5 (five minutes after the application of the acute stressor). Between 0 and 1 minute the rabbit was subjected to an acute stress stimulus based on semen collection ([Serrano-Jara et al., 2025](#)).

For semen collection, males started the training period at 150 days of age. The training sessions were conducted once per week over a period of 2–3 weeks ([Lavara et al., 2011](#)). After training, the males entered the production period.

2.3 Blood parameters

Eighty blood samples were collected from the central auricular artery in two conditions: under heat stress ($THI \geq 27.8$) and non-heat stress ($THI < 27.8$). The samples were collected in 13 x 75 mm tubes with a 3 mL capacity containing potassium salt K_3EDTA (ethylenediaminetetraacetic acid) as anticoagulant. Blood samples were collected using a needle with a diameter of 0.6 mm (23G). Blood was centrifuged at 4000 rpm for 15 minutes to obtain plasma and proceed with the determination of CRP, $TNF-\alpha$, and cortisol. The samples were frozen at $-80^\circ C$ until analysis.

$TNF-\alpha$. $TNF-\alpha$ was measured by commercial ELISA test (Elabscience Bionovation Inc, Catalog Number: E-EL-RB0011, Houston, TX, USA). The distribution of the samples was as follows: 20 (LS), 20 (HS), 20 (LNS) and 20 (HNS).

CRP. CRP was measured by commercial ELISA test (Life Diagnostics Inc, Catalog Number: CRP-10-N, West Chester, PA, USA). A total of 61 samples were recorded: 17 (LS), 16 (HS), 16 (LNS) and 12 (HNS). The rest of the samples were not recorded in the ELISA test.

Cortisol. Cortisol was measured by commercial ELISA test (Cusabio Technology LLC, Catalog Number: CSB-E06956Rb, Houston, TX, USA). A total of 38 samples were recorded: 18 (LS), 12 (HS), 5 (LNS) and 5 (HNS). The rest of the samples were not recorded in the ELISA test.

2.4 Statistical analysis

The correlated response was estimated as the difference between the High and Low lines. Temperature (y_{ijk}) was analyzed with the model:

$$y_{ijk} = \mu + TLS_i + bW_{ij} + m_{ij} + e_{ijk}$$

where μ is the overall mean, TLS_i is the time-line-stress effect with twelve levels (time: minute 0, 1 or 5; line: High or Low; stress: $THI < 27.8$ or $THI \geq 27.8$), b is the regression coefficient, W_{ij} is the covariate weight, m_{ij} is the random effect of male and e_{ijk} is the residual term.

For blood parameters (CRP, $TNF-\alpha$, and cortisol; y_{ijk}) the following model was used:

$$y_{ijk} = \mu + LS_i + bW_{ij} + m_{ij} + e_{ijk}$$

where μ is the overall mean, LS_i is the line-stress effect with four levels (High or Low; stress: $THI < 27.8$ or $THI \geq 27.8$), b is the regression coefficient, W_{ij} is the covariate weight, m_{ij} is the random effect of male and e_{ijk} is the residual term.

All analyses were performed using Bayesian methodology. Bounded uniform priors were used for all effects except for the male effect, considered normally distributed with mean 0 and variance $I\sigma^2_p$. Residuals were *a priori* normally distributed with mean 0 and variance $I\sigma^2_e$. The priors for the variance were also bounded uniform. Features of the marginal posterior distributions for all unknowns were estimated using Gibbs sampling. Inferences

were derived from the marginal posterior distributions. Means, standard errors and actual probability (P) were provided. P refers to the probability that the absolute value of the difference between two levels of a fixed effect will be greater than zero (Blasco et al., 2017). P indicates the probability that the differences are above zero when $H-L > 0$, or below zero when $H-L < 0$. Within a Bayesian framework, the notion of “statistical significance” in the classical sense does not apply; instead, the model directly estimates the probability of the differences being positive or negative. Notably, these probabilities may reach or even surpass 0.90, even in cases where the 95% credible interval still encompasses zero. We consider that there are relevant differences when the P is greater than or equal to 90%. The Rabbit software program developed by the Institute for Animal Science and Technology (Valencia, Spain) was used for all procedures. We used a chain of 60,000 samples, with a burn-in period of 10,000. Only one out of every 10 samples was saved for inferences. Convergence was tested using the Z criterion of Geweke (Sorensen and Gianola, 2002) and Monte Carlo sampling errors were computed using time-series procedures (Geyer, 1992).

3 Results

3.1 Temperature

Figure 1 shows the progression (at minutes 0, 1, and 5) of eyeball temperature both conditions (heat stress and non-heat stress). For all the moments, the Low line showed lower temperatures than the High line, both in the absence and

presence environmental heat stress ($P = 100\%$; P: probability that the difference between the temperatures of both lines at each moment is different from 0).

In the absence of environmental heat stress, at minute 0, the Low line showed a lower eyeball temperature than the High line (36.45°C vs 36.77°C ; $P = 92\%$). At minute 1, temperature tended to be lower in the Low line than in the High line ($90\% > P > 80\%$). No differences were found between the lines at minute 5 ($P = 71\%$).

After seminal collection, between minute 0 and 1, both lines increased in temperature (Low line: 36.71°C and $P = 99\%$; High line: 36.91°C and $P = 90\%$). Between minute 1 and 5, both lines increased their temperatures (Low line: 36.77°C and $P = 71\%$; High line: 36.91°C and $P = 51\%$).

In the presence of environmental heat stress the Low line presented a lower temperature than the High line at minute 0 (37.12°C vs 37.78°C ; $P = 100\%$). After seminal collection, between minute 0 and 1, none of the lines increased their temperature during the first minute (Low line: 37.21°C and $P = 72\%$; High line: 37.84°C and $P = 65\%$). The difference between the lines was maintained at minute 1 ($P = 99\%$). Between minute 1 and 5, only the Low line increased its temperature (37.41°C ; $P = 92\%$) in comparison to the High line (37.92°C ; $P = 72.2\%$). The difference between the temperature of the two lines remained present ($P = 97\%$).

3.2 Blood parameters (CRP, $\text{TNF-}\alpha$, cortisol)

Table 1 shows the differences of correlated response between the lines in CRP, $\text{TNF-}\alpha$, and cortisol levels under conditions with and

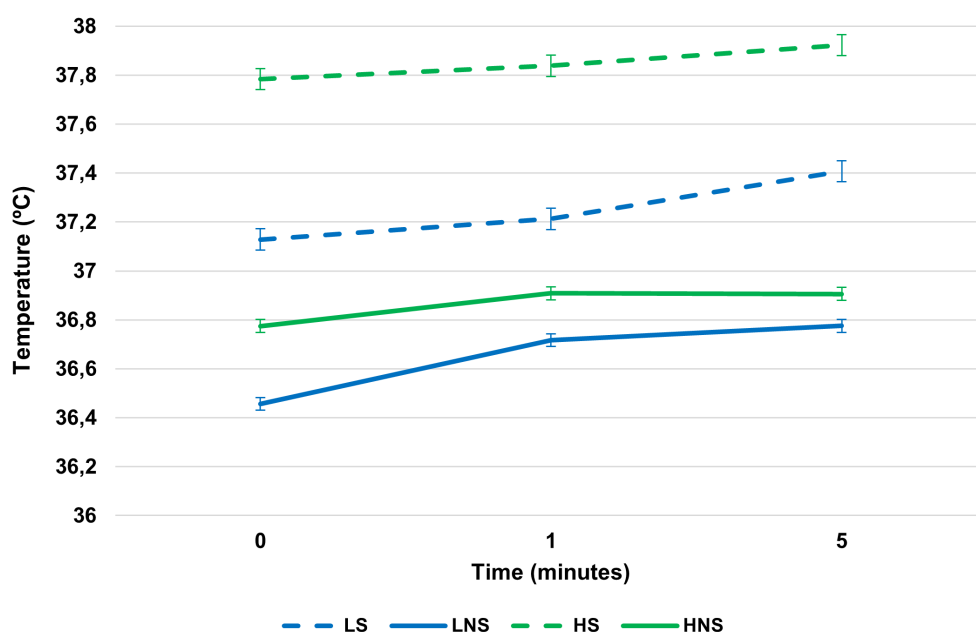


FIGURE 1

Means and standard errors (bars) of the marginal posterior distributions for eyeball temperature, recorded with infra-red thermography, in two rabbit lines with and without heat stress. HS, High stressed line; LS, Low stressed line; HNS, High non-stressed line; LNS, Low non-stressed line. The vertical bars represent the standard error.

without heat stress. CRP levels showed no differences between the lines ($P < 80\%$). The Low line showed lower TNF- α levels in the presence of environmental heat stress ($P > 90\%$), but only a trend ($90\% > P > 80\%$) in the absence of environmental heat stress. Regarding plasma cortisol levels, the Low line showed lower levels than the High line ($P > 90\%$) both in the presence and absence of environmental heat stress.

Table 2 shows a comparison of the results obtained under heat stress and thermal comfort conditions within the same lines. TNF- α showed an upward trend in the presence of environmental heat stress in the High line ($90\% > P > 80\%$). As for CRP, only in the absence of environmental heat stress in the Low line was there a tendency for its concentration to increase ($90\% > P > 80\%$). Cortisol levels did not vary between the presence and absence of environmental heat stress in any of the lines ($P < 80\%$).

4 Discussion

Selecting animals primarily for productivity has been associated with negative side effects in their health, fertility, and immune responses (Rauw et al., 1998). Nowadays, the fight against climate change and the improvement of animal welfare are related challenges that affect livestock farming both socially and scientifically.

Over the course of 17 generations, two rabbit lines have been divergently selected based on the environmental variability of litter size (i.e. phenotypic variance of litter size within each female, after correcting litter size for year-season effects and parity-lactation status). This selection strategy has been proposed as a direct approach to improving resilience traits (Blasco et al., 2017). Several studies have demonstrated that females from the Low line

TABLE 1 Correlated response to selection for resilience in plasma TNF- α , CRP, and cortisol levels in two rabbit lines.

Group	H (ng/ml)	L (ng/ml)	DH-L	HPD95%	P
TNF- α					
HS - LS	69.092	56.438	12.654	-23.817, -0.217	0.98
HNS - LNS	65.655	59.994	5.711	-17.311, 5.604	0.84
CRP					
HS - LS	3.721	3.505	0.216	-0.958, 0.558	0.71
HNS - LNS	3.735	3.914	-0.179	-0.603, 0.997	0.68
Cortisol					
HS - LS	9.771	7.693	1.978	-4626.39, 647.65	0.93
HNS - LNS	11.024	6.985	4.039	-8268.8, 338.22	0.97

HS, High stressed line; LS, Low stressed line; HNS, High non-stressed line; LNS, Low non-stressed line; DH-L, difference between lines; HPD95%, Highest Posterior Density 95% interval, the shortest interval containing 95% of the posterior probability, representing the most credible values of the parameter given the data and model; P, probability of DH-L being >0 when DH-L was positive, or <0 when DH-L was negative.

TABLE 2 Comparison of plasma TNF- α , CRP, and cortisol levels between stressed and non-stressed groups in two rabbit lines.

Group	S (ng/ml)	NS (ng/ml)	DS-NS	HPD95%	P
TNF- α					
HS - HNS	69.092	65.655	3.447	-6.615, 14.687	0.84
LS - LNS	56.438	59.944	3.506	-13.429, 5.833	0.79
CRP					
HS - HNS	3.721	3.735	0.014	-0.822, 0.829	0.51
LS - LNS	3.505	3.914	0.409	-1.188, 0.321	0.85
Cortisol					
HS - HNS	9.771	11.024	-1.253	-5.016, 2488	0.74
LS - LNS	7.693	6.985	0.708	-2.443, 4.182	0.67

HS, High stressed line; LS, Low stressed line; HNS, High non-stressed line; LNS, Low non-stressed line; DS-NS, difference between stress and no; HPD95%, Highest Posterior Density 95% interval, the shortest interval containing 95% of the posterior probability, representing the most credible values of the parameter given the data and model; P, probability of DH-L being >0 when DH-L was positive, or <0 when DH-L was negative.

exhibit superior adaptive capacity under adverse environmental conditions (García et al., 2016; García et al., 2019; Argente et al., 2019).

Our results indicate that, the Low line maintains a lower eyeball temperature compared to the High line, while retaining a normal physiological response to the sperm collection stimulus. Furthermore, the findings show that, in non-heat-stress condition the response to the acute stressor is rapid in both lines, consistent with observations reported in the cited literature (Jaén-Téllez et al., 2021; Serrano-Jara et al., 2025).

Under heat stress, as also reported by De Lima et al. (2013) and Jaén-Téllez et al. (2020), the body temperature of both lines increased. The lower temperature observed in the Low line reflects its superior ability to adapt to adverse environments compared to the High line. In contrast, the lack of a thermal response to semen collection in the High line may be due to the presence of a chronic stress state, which could diminish, delay, or impair its adaptive capacity (Moberg, 2000; McEwen and Wingfield, 2003; Koolhaas et al., 2011).

The improved regulation of body temperature observed in the Low line, selected for resilience, may reflect an enhanced capacity to maintain homeostasis under challenging conditions. This thermoregulatory advantage could be mediated by more efficient neuroendocrine responses to stress, in line with observations in other robustness-selected lines (Biada et al., 2024).

The analysis of stress-associated biomarkers complements the study of temperature by providing insight into the animals' chronic stress status. The consistently lower cortisol levels in the Low line, regardless of environmental conditions, suggest a more adaptive HPA axis response, which may prevent the detrimental effects of prolonged glucocorticoid release. In contrast, the High line appears to exhibit higher baseline activation of the HPA axis, consistent with Argente et al. (2019), which could indicate a reduced threshold for stress activation and a chronic stress profile.

Differences in TNF- α concentrations reinforce this interpretation. Under heat stress, the Low line displayed lower TNF- α levels, suggesting a more controlled inflammatory response. Elevated cortisol levels in the High line may compromise immune competence by suppressing lymphoid activity and impairing the balance between pro- and anti-inflammatory cytokines (Ayyat and Marai, 1997; Liang et al., 2022). This imbalance has been described in other livestock species, where heat stress enhances systemic inflammation and increases susceptibility to infections (Lara and Rostagno, 2013; Lemal et al., 2023). Thus, the interaction between glucocorticoids and cytokines could explain the parallel differences observed in both stress physiology and thermoregulation.

Regarding CRP, no differences were found between lines in our study. The discrepancies with Argente et al. (2019) and Beloumi et al. (2020), where the Low line exhibited lower CRP levels, might be related to differences in sex, physiological stage, or timing of sampling, as has been observed in rats (Nunomura, 1992; Balog et al., 2015). It is also possible that CRP, unlike other acute-phase proteins such as haptoglobin, is less sensitive to heat stress in rabbits, as also reported by Argente et al. (2014).

Altogether, these results suggest that resilience-selected animals (Low line) may mitigate the negative effects of heat stress by combining

better thermoregulatory efficiency with a more adaptive HPA axis and a moderated inflammatory response. This integrative response could represent a physiological mechanism underpinning resilience, similar to findings reported in other species exposed to heat stress (Laghuaouta et al., 2024; Sejian et al., 2018).

In this research, the assessment of stress relied on three biomarkers (CRP, TNF- α , and cortisol). These markers provide valuable insights into immune and endocrine responses, but the inclusion of additional indicators such as haptoglobin, oxidative stress parameters, or corticosterone, the primary glucocorticoid in rabbits (Bush, 1953), would allow for a more comprehensive understanding of the physiological mechanisms underlying resilience to heat stress. Although cortisol remains a relevant and widely used hormone for evaluating stress in rabbits (Szeto et al., 2004; Verga et al., 2007), complementing its measurement with corticosterone could further refine the interpretation of the stress response.

5 Conclusions

The biomarkers evaluated in this study, together with infrared thermography, represent useful tools for assessing acute stress responses both under heat stress and comfort conditions.

These results highlight the value of selecting for functional traits such as resilience in improving animals' adaptive responses to heat stress. Thus, incorporating these criteria, specifically selection for litter size homogeneity, into breeding programs contribute to both enhanced animal welfare and sustainable livestock production.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was approved by General Directorate of Agriculture, Livestock and Fisheries of the Generalitat Valenciana with code 2022/VSC/PEA/0226. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

DS-J: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. IA: Conceptualization, Methodology, Writing – review & editing. GR: Conceptualization, Methodology, Writing – review & editing. MA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – review & editing. MS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing. MG: Conceptualization, Data curation, Formal analysis, Funding

acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research and/or publication of this article. This study forms part of the AGROALNEXT programme (AGROALNEZT/2022/037) and was supported by MCIN with funding from European Union NextGenerationEU (PRTR-C17.I1) and by Generalitat Valenciana.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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