The immune-neuroendocrine system, a key aspect of poultry welfare and resilience

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ABSTRACT There is increasing societal concern regarding the negative impact of intensive poultry production on animal welfare, human health, and on the environment. This is leading to the inclusion of animal welfare as an imperative aspect for sustainable production. Certain environmental factors may challenge domesticated birds, resulting in poor health and welfare status. Resilience is the capacity to rapidly return to prechallenge status after coping with environmental stressors, thus resilient individuals have better chances to maintain good health and welfare. Immune-neuroendocrine system, thoroughly characterized in the domestic bird species, is the physiological scaffold for stress coping and health maintenance, influencing resilience and linking animal welfare status to these vital responses. Modern domestic bird lines have undergone specific genetic selective pressures for fast-growing, or high egg-production, leading to a diversity of birds that differ in their coping capacities and resilience. Deepening the knowledge on pro/anti-inflammatory milieus, humoral/cell-mediated immune responses, hormonal regulations, intestinal microbial communities and mediators that define particular immune and neuroendocrine configurations will shed light on coping strategies at the individual and population level. The understanding of the profiles leading to differential coping and resilience potential will be highly relevant for improving bird health and welfare in a wider range of challenging scenarios and, therefore, crucial to scientifically tackle long term sustainability.

Key words: welfare, poultry production, immunology, stress, neuroendocrinology

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LINKING WELFARE WITH RESILIENCE; PHYSIOLOGICAL BASES

Poultry meat and eggs are among the world's animal protein sources in highest demand, a demand expected to continue to increase (FAO, 2015; Augère-Granier, 2019). In parallel, societal concerns regarding intensive production systems have also increased (Augère-Granier, 2019; Koutsoumanis et al., 2019) mainly due to its potential negative impact on animal and human health and on the environment (Murphy et al., 2017; Augère-Granier, 2019). Such concerns led to include animal welfare as an imperative aspect in production (Mellor, 2016; Buller et al., 2018), even leading to its recognition by the United Nations as a pillar for sustainable production (Committee on World Food Security, 2016, 2021).

Along poultry production, certain management practices or environmental factors i.e., extreme temperatures (either high or low), transport, alterations in the photoperiod or in the social groups and structures, etc., may challenge birds leading to a stress-associated loss in the homeostasis (Nazar and Marin, 2011; El-Edel et al., 2015; Nazar et al., 2015b; Colditz and Hine, 2016; Carrasco et al., 2019; House et al., 2021). Responses aimed at re-establishing the homeostatic lost conditions demand resources (Wingfield, 2013; Colditz and Hine, 2016; Giayetto et al., 2020) and could lead to negative consequences on birds' health and welfare (Colditz and Hine, 2016; Calefi et al., 2017; Nazar et al., 2018; Carrasco et al., 2019). Resilience has been defined as the capacity to rapidly return to prechallenge status after coping with infectious or other environmental stressors (Wingfield, 2013; Colditz and Hine, 2016; Berghof et al., 2019). Resilient birds should invest less energy in coping and recovering from stressors, thus more energy will be available for body maintenance and

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normally will result in improved performance (Wingfield, 2013; Colditz and Hine, 2016). Resilience and coping abilities are, therefore, traits of outmost importance in poultry production systems specially if aiming at prioritizing animal welfare and health.

The immune-neuroendocrine (INE) system is thoroughly characterized in poultry species (Kaiser et al., 2009; Davison et al., 2011; van der Eijk et al., 2020; House et al., 2021; Scanes, 2021). The functioning of this system is supported by main axes; the Hypothalamus-Pituitary-Adrenal (HPA) (Kaiser et al., 2009; Oakley et al., 2014; Ashley and Demas, 2017), the Sympathetic-Adrenergic (SA) (Kaiser et al., 2009; Ashley and Demas, 2017) and, the Microbiota-Gut-Brain (MGB) (Stanley et al., 2013; Calefi et al., 2016; Kogut, 2019). Any of these axes can sense the changes and/or alterations induced by environmental challenges or activate the precise mechanisms to cope with them (Oakley et al., 2014; Ashley and Demas, 2017). Consequently, the INE system is the main physiological scaffold for coping (Kaiser et al., 2009; Calefi et al., 2016; Ashley and Demas, 2017), influencing resilience, and linking welfare status to this vital INE ability to withstand challenges (see Figure 1). For example, the HPA axis is involved in stress responses, being elevated glucocorticoids (corticosterone, mainly) a classic indicator of its activation. These molecules are partly responsible for behavioral alterations aimed at coping with stressors, but also alter individuals' pro- and anti-inflammatory mediators' balance, further determining the ability to withstand infectious challenges (Shini et al., 2010; Crhanova et al., 2011; Scanes, 2016).

Not all birds respond or cope in the same manner, leading to differential susceptibilities. This diversity of responses is evidenced in immune-neuroendocrine phenotypes (Sternberg et al., 1989; Elenkov, 2008) described for laying hens and Japanese quail (Nazar et al., 2015a,2017), and that co-exist in the populations confirming that different individuals rely on different INE potentials. These phenotypes, represent neuroendocrine and immunological phenotypes that differ across groups of individuals within the same population (Sternberg et al., 1989; Elenkov et al., 2008; Nazar et al., 2015a,2017). Because of INE phenotypes existence, individuals within the same population react physiologically different to the same environmental challenge and may invest (or require) differential amount of resources in recovering the lost homeostasis. This way, individuals may encounter the same challenge (altered temperatures, a predator, even weighting routines, etc), but the response will be highly tight to their actual potential of response (Buehler et al., 2010; Nazar et al., 2017). It is highly relevant, for research efforts to come, to deeply understand basal and challenged INE configurations, to scientifically depict the spectrum of potential responses and susceptibilities in the main domesticated poultry species (chickens and hens, turkeys, quail, ducks, and geese) we raise today.

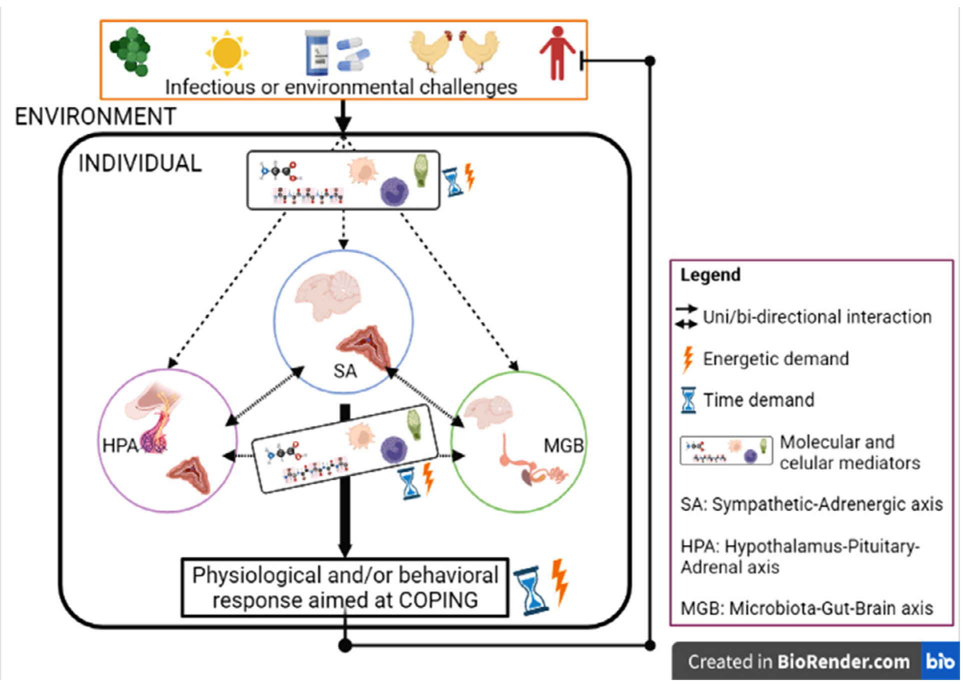

Figure 1. Schematic flowchart demonstrating immune-neuroendocrine activation and its connection to poultry resilience and welfare. Environmental challenges induce changes and alterations in molecular mediators and/or cells (homeostasis lost) which are sensed by one or more immune-neuroendocrine axes (HPA, MGB, and/or SA). Communication through molecular mediators and/cells is established among these axes to process the perceived stimulus. Later, the precise mechanism to cope with the challenge is activated, leading to a physiological and/or behavioral response to recover homeostatic conditions. Each stage described is time and resource consuming. Individuals investing less energy in coping will solve threats with lower demand than individuals investing more energy (less resilient). In resilient birds, energy will be available for body maintenance, resulting in improved performance. Less resilient birds may consume all their energetic budget in coping, thus running out of resources for other traits, i.e., body maintenance, reproduction, health, ultimately leading to welfare impairments.

WELFARE AND STRESS RESPONSES

The latest scientific definitions of animal welfare consider that animals have positive and negative experiences, and focus on reaching a balance among them with the goal to 'a life worth living' (Mellor, 2016; Buller et al., 2018). Safeguarding the 5 freedoms (Broom, 2011) 1) from hunger and thirst, 2) from discomfort, 3) from pain, injury or disease, 4) to express normal behavior and freedom of movements, and 5) from fear and distress, has long been considered the main pillar for ensuring animal welfare. Key concepts included in these freedoms, namely disease, discomfort, fear, and distress, evidence the involvement and relevance of the INE system to guarantee animal welfare. Production systems may expose birds to negative experiences or challenging situations jeopardizing such freedoms. Literature informs on a wide variety of sources that can challenge each of these freedoms, that is, maintenance chores, environmental temperature alterations, weighting and vaccination routines, change of housing, social group alteration, etc. (Leone and Estévez, 2008; Nazar et al., 2015b; Colditz and Hine, 2016; Carrasco et al., 2019).

However, major welfare impairments only occur when these situations overlap, are repeated, or are sufficiently sustained in time to induce in the birds a chronic stress status (Scanes, 2016; Nazar et al., 2018; Carrasco et al., 2019). This scenario involves long recovery periods, due to the persistence of both, the challenge and the derived effects of main INE axes that are activated (Ashley and Demas, 2017; Calefi et al., 2017; Kogut, 2019). The sustained activation of the HPA axis, for example, would lead to chronically increased concentrations of glucocorticoids. In the long run, glucocorticoids exert immunosuppressive effects due to immune cells (different subtypes of lymphocytes, mainly) death and mediators' unbalance (Shini et al., 2010; Davison et al., 2011; Scanes, 2016). In practical terms, immunosuppression will render individuals potentially defenseless against pathogens that would otherwise mean no threat, impairing their welfare and hence their performance. Despite of this well-known response, scientific literature shows that there is great diversity on how poultry species respond to challenges, from daily management routines, or the social context, to pathogens (Ericsson et al., 2014; Scanes, 2016; Campderrich et al., 2017; Nazar et al., 2017). Individual birds abilities to adapt to such challenges relies on specific INE response which has been shaped by domestication and artificial selection pressures (Rubin et al., 2010; Tixier-Boichard et al., 2011).

Chronic stress, as described in the previous paragraph, occurs when demands are sustained long enough to lead to birds' welfare impairments. However, the stress response have persisted along evolution because of its beneficial effects on the short term (Heijnen, 2007; Colditz and Hine, 2016). Acute stress responses are generally associated to resource mobilization aimed at obtaining energy and activating physiological and behavioral mechanisms to cope with the stressful threat (Zimmer and Spencer, 2014; Seebacher and Krause, 2017) i.e., escaping from a predator, finding refugee in adverse climatological conditions or even exploring a new environment (Buehler et al., 2010; Zimmer and Spencer, 2014; Herborn et al., 2018). In between chronic and acute scenarios, an intermediate spectrum of responses exists in which individuals can administrate and use their resources remaining healthy and productive (Dhabhar, 2009; Scanes, 2021). Thus, the extent to which one individual can withstand challenges without detriment in its welfare status will be defined by its resilience capacity, which is not necessarily uniform due to the INE phenotypic variability. Further knowledge should aim at defining the conditions for maintaining production birds under our care in the mentioned intermediate spectrum, thus maximizing resilience and welfare. This research should constitute the bases for rearing and management programs to tackle sustainable poultry production in the long term.

THE DOMESTIC FOWL, AN EXAMPLE OF MODELLED IMMUNE-NEUROENDOCRINE RESPONSE POTENTIAL

The domestic fowl was domesticated 8,000 years ago (Tixier-Boichard et al., 2011). Birds have been exposed to human-driven selection first, followed by a more recent intense genetic selection for productive traits (meat or eggs), leading to phenotypic changes in morpho-physiological, behavioral and INE characteristics (Rubin et al., 2010; Tixier-Boichard et al., 2011). Modern commercial domestic fowl lines grow faster, become sexually mature earlier, lay more/larger eggs, show reduced fearfulness and increased social stress tolerance (Estevez et al., 2003, 2007; Campler et al., 2009; Wright et al., 2012; Ericsson et al., 2014). However, intense genetic selection also led to undesirable side-effects. Growth rate, skeletal problems and ascites have great impact on meat chicken welfare (Griffin and Goddard, 1994; Decuypere et al., 2000; Estevez, 2007). Selection for egg-production led to increased problems with cannibalism and feather pecking (Cheng, 2010), resulting in injuries and higher mortality, as well as to difficulties to recover from pathologies (Simon et al., 2016). Besides these heavily selected, a variety of rustic lines, not selected dual purpose, as well as medium- and slow-growing lines cover almost the whole spectrum diversity in growth rate and associated physiological characteristics. In these, the negative consequences of genetic selective pressures have been less intense (Bokkers and Koene, 2004; Castellini et al., 2016).

As previously mentioned, domestic fowl welfare status is heavily linked to the INE responses that allow individuals to adapt to and cope with a great range of environmental conditions (Kaiser et al., 2009; Calefi et al., 2016; Ashley and Demas, 2017), and better adaptability leads to higher resilience (Wingfield, 2013; Colditz and Hine, 2016; Berghof et al., 2019). The genetic selection applied during the last century to domestic fowl lines has led to an ample diversity of birds that are remarkably different in their capacity to withstand health, social and environmental stressors. The INE basal configuration and response potential depends on complex pro/anti-inflammatory molecules balance, humoral/cell-mediated immune responses, hormonal regulations, intestinal microbial communities, and mediators. Altogether, these components determine the coping ability of domestic fowl lines depending on the selection process they have undergone. Understanding the interrelationship among the diversity in INE profiles with coping and resilience is crucial to comprehend the key physiological aspects leading to stronger and healthier birds.

Coping involves behavioral and INE coordination, including prioritization of energy expenditure when challenges are sustained in time or presented simultaneously (Colditz and Hine, 2016; Giayetto et al., 2020). If individuals encounter difficulties in coping, or if failing to do so, performance indicators (Quinteiro-Filho et al., 2012; Marin et al., 2014) and health status (Kogut and Arsenault, 2016; Carrasco et al., 2019) can be compromised leading to poor welfare (Colditz and Hine, 2016; Calefi et al., 2017; Nazar et al., 2018; Carrasco et al., 2019). These problems are not homogenous in domestic fowl lines. Egg laying lines, compared to meat lines, show higher HPA activation in response to chronic feed and water restriction (Hocking et al., 1993), more stress-induced vocalizations in response to repeated isolation (Saito et al., 2005), and develop a more proinflammatory immune response (Simon et al., 2016).

The MGB axis plays a key role in health maintenance and animal welfare (Carrasco et al., 2019; Kogut, 2019; van der Eijk et al., 2020) being also a major modulator of the INE interplay, although it was not included in the INE matrix until a couple of years ago (Kogut and Arsenault, 2016; Borda-Molina et al., 2018; Kogut, 2019). A 'healthy gut' regulates not only the local intestinal homeostasis, but also regulates other systemic organs that support host's ability to cope with a variety of environmental (including infectious) stressors (Crhanova et al., 2011). Together with the HPA and SA axes, the MGB axis appeared as a promising research avenue for increasing birds' resilience for a sustainable production (Collins et al., 2012; Oakley et al., 2014; Kogut, 2019). In the domestic fowl, gut microbiota transplantation shows immediate and long-term effects on feather pecking and on INE mediators concentration (van der Eijk et al., 2020). Infectious and environmental challenges impact on the MGB axis, affecting the microbiota diversity and composition depending on the gastrointestinal segment (Borda-Molina et al., 2018; Carrasco et al., 2019; Hubert et al., 2019; Kogut, 2019). These challenges can find its origin in the diet and additives, in moving between facilities, in the use of antibiotics, etc., and may act in a nonexcluding manner (Costa et al., 2017; Pineda-Quiroga et al., 2017; Borda-Molina et al., 2018; Kogut, 2019). Altered microbiota leads to impaired capacity to modulate local and systemic INE responses, and to harvest energy from nutrients (Kogut and Arsenault, 2016; Costa et al., 2017; Kogut, 2019). Birds' performance is then altered and welfare is impaired because pathologies' severity and mortality are increased (Casewell et al., 2003; Gadde et al., 2018; Zahoor et al., 2018), that is, Salmonellosis or Necrotic enteritis caused by *C. perfringens*.

The activation of each of the so far mentioned INE axes in response to challenges depends on genetic background and on birds' phenotypic variability. Individual susceptibility leads to different energetic budget to cope with challenges (Sternberg and Hill, 1989; Senner et al., 2015; Nazar et al., 2015a), differentially impairing welfare and productive relevant traits. The characterization of the budgets on which each poultry species we raise rely, as well as the potential effects on this budget of the variety of challenges birds may face along rearing, is a vacant area worth deepening in future research.

DIFFERENT POULTRY SPECIES, DIFFERENT 'STATES-OF-THE-ART'

Different poultry species and genetic lines are reared with productive purposes today and the extent to which scientific knowledge is available for each group differs. Hens and broilers (*Gallus gallus*) are the paramount model for poultry, being the most deeply studied and characterized groups in this sense, as evidenced in the previous section. Although not studied in such a great detail, Quail (*Coturnix coturnix* and *coturnix japonica*) and Turkeys (*Meleagris gallopavo*) have been also studied: the interlink between some INE mediators and productive/behavioural indicators have been described (Huff et al., 2003,2005; Hayward and Wingfield, 2004; Cockrem, 2007; Zimmer et al., 2017), and HPA, SA and MGB axes effects on immune mediators have been characterized in basal and stressful situations (Fair et al., 1999; Cockrem, 2007; Hazard et al., 2008; Nazar et al., 2015a; Kraimi et al., 2019; Scanes et al., 2020a,b; Batool et al., 2021). Behavioural and physiological interlinks are better characterized for quails than for turkeys, proving for example, that absence of gut microbiota reduces emotional reactivity in challenges involving fear and social perturbation (Kraimi et al., 2018). Studies on Ducks' welfare (*Anas platyrhynchos, Cairina moschata* and hybrids) have increased during the last decades as evidenced in recent reviews (Liao et al., 2021; Makagon and Riber, 2022), but detailed interlinks between INE system and welfare are just starting to be unraveled (Ismoyowati et al., 2018; Mohammed et al., 2019; Voit et al., 2020). Lastly, Geese (*Anser anser* and *Anser cygnoides*) are the less scientifically studied group, in which welfare is being explored since a decade (Scheiber et al., 2015; Tremolada et al., 2020; Voit et al., 2020) but INE components have not been characterized in relation to welfare yet.

The knowledge asymmetry on each of the mentioned poultry species has a lot to do with their relevance as a production species, with the domestic fowl being in this sense the most relevant species from the economic standpoint. For future research, independently from the poultry species, it would be important to develop integrative experimental designs. Including behavioral, productive, and INE variables in the same project would lead to construction of a wider perspective in poultry (animal) welfare, better preparing researchers and stakeholders to achieve sustainable production prioritizing the welfare of an animal as a whole.

CLOSING REMARKS

Including INE variables in welfare studies will contribute to filling the existent gap in the understanding of the immunological and neuroendocrine substrates that leads to coping abilities. Research will be able to determine the effects that genetic selective pressures for performance traits have had on pro/anti-inflammatory milieus, humoral/cell-mediated immune responses, hormonal regulations, intestinal microbial communities, and mediators, thus shaping INE responses in the domestic birds we raise today. This knowledge will reveal, both at the individual and at the population level, the differential basal arrays that confer diversified stress coping and resilience abilities in egg- or meat-genetic lines of domestic birds and the range of genetic lines in between. This information will be key to develop future strategies to improve resilience for sustainable poultry production in challenging scenarios and in its most contemporary sense (Committee on World Food Security, 2021), which includes welfare as an essential component.

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DISCLOSURES

Authors confirm they have no competing interests to declare.

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