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The Adaptive Sex in Stressful Environments

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Abstract :

The impact of early stress on juvenile development has intrigued scientists for decades, but the adaptive significance of such effects remains an ongoing debate. This debate has largely ignored some characteristics of the offspring, such as their sex, despite strong evolutionary and demographic implications of sex-ratio variation. We review recent studies that examine associations between glucocorticoids (GCs), the main class of stress hormones, and offspring sex. Whereas exposure to GCs at around the time of sex determination in fish consistently produces males, the extent and direction of sex-ratio bias in response to stress vary in reptiles, birds, and mammals. We propose proximate and ultimate explanations for most of these trends.

Highlights

► Offspring sex ratios have been shown to correlate with environmental stressors and maternal stress in many vertebrate species. ► There is an adaptive advantage for parents to produce the sex that is more likely to survive and reproduce in a future hazardous environment. ► In the fastest life histories, there is more likely to be a close good match between the environment around sex determination and the future environment of the offspring. ► GCs are key messengers of environmental contexts that likely influence the sex-determination processes of various species. ► A combination of field and laboratory studies will be necessary to understand the extent to which stress influences offspring sex from conception to birth.

Keywords : sex determination, sex ratio, maternal effect, adaptive response, glucocorticoids

Sex-stress interaction

Among vertebrates, sex can be determined by **environmental sex determination (ESD,** see Glossary), **genetic sex determination (GSD**) or the interaction of both. The phylogenetic distribution of GSD and ESD indicates that transitions between these types of sex determination have occurred many times [1]. While mammals and birds have only GSD, sex-determining mechanisms have high evolutionary plasticity in fish, reptiles and amphibians. Nevertheless, the sensitivity of the undifferentiated gonad to circulating sex hormones is a common feature shared by many vertebrates, including those with GSD [1]. Over the years, the hypothesis that glucocorticoids (GCs), the main class of stress hormones (Box 1), would interact with sex hormones to influence the sexual fate of the gonad has emerged following numerous laboratory studies. In parallel, recent technological advances in stress measurements (Box 1) have allowed the quantification of GCs in free-ranging animals, enabling the discovery of a link between GC levels and sex ratio biases in natural environments. Given GCs act to convert stressful stimuli into physiological signals, they are promising candidates for the translation of environmental, social and state-dependent factors into adaptive sex allocation.

Here we review the body of evidence that GCs influence **sex determination** and bias the **offspring sex ratio** across vertebrates (Figure 1). This can happen directly in species with ESD or indirectly through maternal effects. We then explore the potential evolutionary causes explaining why, in a stressful environment, one sex would be more adaptive than the other in animals with either ESD or GSD.

Direct influence of glucocorticoids on sex determination or sex differentiation

In fish, studies conducted to date have tended to show that at sub-optimal temperatures (*i.e.* very high or very low), low pH, continuous lighting or high density – each of which can be

considered to be a stressful condition [2] – more males are produced (Figure 1). In fish, sex determination can occur at different stages of the life cycle: at fertilization or later in development (egg or larval stage). The undifferentiated gonad of fish is extremely labile and sensitive to external factors [1]. In recent years, the link between stressful environmental conditions and GCs has been established as being a major factor influencing sex determination in fish. For instance, high **cortisol** levels at the egg stage can override genetic sex in species with GSD such as the medaka (*Oryzias latipes*) [3] and rainbow trout (*Oncorhynchus mykiss*) [4]. High temperatures during the larval stage can trigger higher cortisol production that directly influence the sex of individuals in the Pejerrey (*Odontesthes bonariensis*) [5] and Japanese flounder (*Paralichthys olivaceus*) [6]. Other stressful conditions applied at the larval stage such as constant light exposure [7], stressful tank color [8] and high fish density [9] activate the cortisol synthesis pathway and lead to a higher production of males in various fish species (Figure 1). Although this has not been formally tested in natural conditions with controlled quantities of cortisol, administering cortisol to three-spotted wrasse (*Halichoeres trimaculatus*) induced a female-to-male sex change [10]. In all these examples, more males are produced when stress is applied during the critical period of sex determination or **sex differentiation**, affecting the **primary sex ratio** (PSR) (Box 2).

In crocodilians, low temperatures over the egg laying period produce an all-female population, but in lepidosauria (lizards and snakes) and testudines (turtles) temperature sex-determination is species-specific [11]. When stressed by suboptimal temperatures, **corticosterone** production rises, even with a relatively small temperature increase, as demonstrated in alligator lizards (*Elgaria*) [12]. However, the effects of corticosterone exposure on the sex of reptilian offspring has rarely been studied and the few results available are not as clear as for fish (Figure 1). Although, investigation of gene expression of the key genes (*POMC* and *CRH-BP*) involved in the GC production cascade and regulation

showed an association between high temperature, stress and feminization in the Australian central bearded dragon (*Pogona vitticeps*) [13], another recent study reported a direct link between epigenetic mechanisms and temperature-dependent sex determination in the red-eared slider turtle (*Trachemys scripta*) [14], ruling out GCs as an essential factor, at least in this species. Experimentally introducing corticosterone to developing eggs affected the sex ratio of two lizard species (*Amphibolurus muricatus* and *Bassiana duperreyi)* in an opposite pattern [15] (Figure 1), but did not affect sex ratio of the mallee dragon, *Ctenophorus fordi* [16]. A recent study on the broad-snouted caiman, *Caiman latirostris*, exposed eggs to a synthetic GC in an attempt to influence the sex ratio of embryos already exposed to high temperature (that produce 100% males), the authors were unsuccessful at deviating sex-ratio in favour of females [17]. This suggests either that GCs cannot override the temperature effect or that, in caiman, high levels of GCs would produce male-biased clutches anyway as observed in fish (an hypothesis not evaluated by the authors). More studies are needed to understand if temperature can trigger endogenous production of GCs at the period of reptile sex determination.

Influence of maternal glucocorticoids on offspring sex ratio

Mother-to-offspring GCs transmission is an evolutionarily conserved mechanism found across vertebrate species [18] and is one of the most studied factors in the maternal effect literature [19,20]. However, studies on the relationship between maternal GCs and sex ratio in fish are, to date, lacking. Three different studies investigated the link between maternal stress and sex of reptiles' species with different degree of sex-sensitivity to temperature. Two studies on the common lizard (*Lacerta vivipara)* and the eastern fence lizards (*Sceloporus undulatus*) artificially exposed gravid females to high corticosterone concentration, with no

reported sex-ratio bias [21,22]. In *Amphibolurus muricatus*, a slightly higher percentage of females was detected in clutches of mothers exposed to high corticosterone concentration [23].

In birds, GCs play an important role in sex-ratio biases (Figure 1). Initial studies in captive and free-ranging species showed that elevated levels of maternal GCs are associated with female-biased sex ratios [24–27]. These studies used implants to increase corticosterone levels before nesting and suggested that maternal corticosterone influences PSR. In addition, elevated maternal corticosterone levels can induce higher mortality in male offspring later in development, affecting **secondary sex ratio** (SSR) [28]. However, recent studies show that the picture is more complex than initially thought: females with elevated corticosterone levels produce more male offspring in Gouldian finches (*Erythrura gouldiae*), zebra finches (*Taeniopygia guttata*), chickens (*Gallus gallus*), and ovenbirds (*Seiurus aurocapilla*) [29–32]. Corticosterone injections to female chickens 5 h prior to the expected time of ovulation biased sex ratio towards males [31], whereas injections one hour later biased sex ratios towards females [33]. More work is needed to determine whether this unexpected difference is biologically significant. Most avian studies have been performed in controlled conditions and, the three-way association between environmental stressors, maternal corticosterone, and PSR remains to be investigated.

In many species of mammals, food deprivation and other environmental perturbations during gestation are typically associated with female-biased sex-ratios at birth [34]. However, results from studies that have measured maternal physiological stress are variable (Figure 1). While some studies have shown a positive relationship between maternal GC levels and female bias in the sex ratio [35–39], others have shown a negative relationship [40–42], or no relationship at all [43–48]. Over half of all those studies have been conducted in rodent species (Figure 1). In this group, results are still mixed, but the direction of the pattern, when

present, is rather homogeneous: four out of five studies show a decrease in the proportion of male offspring at birth as maternal GCs increased (Figure 1). In humans, a variety of *a priori* stressful events, ranging from terrorist attacks [49] to death of a close family member [50] were associated with decreases in the proportion of male births, but only two studies measured mother's cortisol with different results (Figure 1). One recent study investigating the link between GC levels of twenty mother howler monkeys (*Alouatta pigra*) and forest fragmentation [41] showed that females always gave birth to females when their fecal GCs were below a threshold of 200 ng. g^{-1} around the time of conception (n = 16), while, above this threshold, they consistently produced males (n = 19). If future work with a much larger sample size confirms this extraordinary pattern, we should worry about the possible impact of anthropogenic pressures on sex ratios of animals.

Timing of sex ratio and glucocorticoid measurements

The sex ratio can vary in response to stress at several developmental time points. Sex-ratio bias can occur around the time of conception and sexual differentiation (affecting the PSR), or during late stages of development through differential mortality (affecting the SSR) (Box 2). This differential mortality is likely to have higher fitness costs, especially in monotocous species (producing only a single offspring at a time), since it implies loss of offspring after maternal resources have already been invested. Thus, low-cost mechanisms of offspring sex-ratio adjustment around the time of sex determination and differentiation are more likely to evolve (Box 2).

The relationship between stress at the time of sex determination or differentiation and PSR has been mainly studied in fish and birds (Figure 1). In fish, high GCs at this developmental point led to a PSR biased toward males. Avian meiosis can be influenced by maternal GCs in response to environmental stress, but the timing of the increase in GCs

appears critical in determining the sense of the sex-ratio bias [31,33].

In most reptiles, the undifferentiated gonads are sensitive to environmental factors during the middle third of the incubation period and it has been reported that maternal steroids in the eggs can decline by more than 90% before the sex is determined [11,51]. It is thus possible that most GCs from maternal origin would be metabolized before sex differentiation and that the remaining amount (as little as 10% of the original present) would be insufficient to influence sexual steroid production, explaining why most studies did not report an effect. The two studies that reported an effect experimentally introduced corticosterone into the egg, probably affecting PSR and led to male sex differentiation [15,17]. On the contrary, when more females were produced in *Amphibolurus muricatus*, the authors proposed that it was through differential mortality of the sexes, suggesting two distinct mechanisms [15]. An experiment evaluating endogenous GCs production at the time of sex determination is now badly needed.

In mammals, the relationship between maternal GC levels and PSR remains unexplored since most studies measure the sex ratio at birth (Figure 1). Several studies, however, support the idea that stress occurring around the time of conception plays a key role in sex determination and even sex differentiation (Box 2). Maternal GCs are generally measured around conception in mammals (Figure 1), but this does not provide insight into when and how GCs act. We cannot discard the possibility that the effects of stress on sex ratio may be delayed rather than immediate. Male fetuses are generally more susceptible to food shortages or other forms of environmental harshness during the last stages of gestation [52]. At the moment, it is still unclear whether such sex differences in mortality are the product of sexual selection (faster growth and larger energetic requirements in males) or the result of adaptive manipulation of the sex ratio by mothers, or a combination of the two. Thus, studies that measure sex ratio at birth can confound two different process: an adaptive effect of

maternal stress near conception on offspring sex ratio and passive consequence of maternal stress on sex-specific fetus mortality. Orzark et al. [53] recently showed that 3- to 6-day-old embryos produced by assisted reproduction in the USA were equally likely to be male and female and while natural abortions during the first trimester were biased towards females, second- and third trimester abortions show a strong bias towards males. This suggests that the direction of sex ratio skews in response to maternal stress could change during gestation.

Adaptive significance

Some cases discussed above may be adaptive, meaning that an animal's tendency to develop as a given sex, after experiencing stress directly or indirectly (through mother's influence), is or has been, under positive selection. If stress-related changes in sex ratio are under positive selection, this implies that one sex would have a higher fitness in stressful conditions (Figure 2) or that maternal stress modifies the relative costs of producing male and female offspring. Indeed, in the absence of any relationship between maternal stress and the relative fitness of male offspring and female offspring, potential costs of reproduction may favor the production of the less costly sex by stressed females. In practice, demonstrating adaptive significance is not easy because fitness is often difficult to measure, especially in the wild. Furthermore, GCs and maternal GCs may be correlated with other physiological traits that are directly involved in adaptive manipulations of sex ratios [54]. The crossover patterns shown in Figure 2 have not yet been tested in studies investigating direct links between GCs and sex ratio. It is more surprising that potential adaptive explanations are often ignored (e.g. [33,35]). We discuss here potential adaptive explanations for most trends observed in Figure 1.

Environmental predictability

GCs around sex determination or differentiation may provide a 'weather forecast' of the

environmental conditions where individuals are likely to live in the future. Related to this idea is the concept of external **predictive adaptive response** (PAR) [55]. Theoretical work shows that external PAR should only be favored by selection where the association between early- and later-life environmental conditions is strong [55]. This is most likely to be true for animals with a fast life-history strategy (short lifespan, early maturity, high fecundity and low per capita investment per offspring)[19]. There is increasing evidence that environmental predictability can determine the strength of selection for sex ratio adjustment [56]. For example, greater sex ratio adjustment is seen in ungulates with shorter gestation periods [57] and primates with shorter maturation times [58], possibly because it is easier for parents to predict the amount of energy they would have available for rearing offspring at the time of conception. Fish and birds have, on average, shorter incubation period than reptiles (Figure 3), which could explain why GCs play a more important role in the process of sex ratio adjustment in the former than in the latter. While the absolute proportion of studies reporting stress-related biases in the sex ratio may over-estimate the true frequency of GCs effects, since positive results are more likely to be published than negative ones [59], the relative proportion within groups of vertebrates should not be affected. The influence of GCs on the sex ratio appears to be correlated with the length of the prenatal period across the groups of vertebrates (Figures 1 and 3), but this is not always the case within groups. For example, marsupials and rodents have very short gestation periods compared with primates, but the absence of relationship between maternal GCs and sex-ratio has been reported in each group (Figure 1). It is possible that the adaptive potential of maternal stress extends well beyond simply a match between maternal and offspring environment [60].

Integrating stress in the Charnov-Bull model

Theoretical models developed by Charnov and Bull [61] predicted that selection should favor

ESD over GSD if 1) the environment differentially affects the fitness of male versus females, so that the sex produced is the better adapted to a given environment, 2) individual has little control on the environment it will experience, 3) the environment is patchy, so that all sexes are produced. It results that in optimal conditions (*i.e.* those that allow long term growth and survival) the sex that will have the greatest absolute fitness benefits will be favored and that in harsh conditions, the sex that will be "less costly" to develop will thrive [62]. With fish, developing in stressful conditions would lead to a sex ratio bias towards males. This prediction involves intrinsic sex difference in life-history traits related to reproduction where males generally mature earlier than females and where the cost of producing sperm is much lower than the cost of developing eggs (review of 98 fish species, [63]). In addition, females generally grow bigger than males [64], highlighting that females may require a higher energy input. So, in a low quality patch with limited resources, developing as a male would be adaptive as it would be physiologically less costly and would allow reproducing quicker [65]. At least for fish, cortisol would play an essential role as being a physiological transducer providing information of the patch quality since fasting induces cortisol production [66].

Social factors

Social factors like hierarchical rank shape GC levels in many species of all the above described taxa [67–69]. In hermaphroditic fish, such as clownfish species or the bluehead wrasse (*Thalassoma bifasciatum*), an abrupt change in the established hierarchy triggers sex-change, and cortisol regulation likely plays a pivotal role in this process [69,70]. Social complexity of many species of birds and mammals often leads to multiple selection pressures on sex ratio adjustment, potentially operating in different directions [71]. The Trivers-Willard hypothesis [72] states that females in good condition, including those of high social rank, should produce more male offspring in species where sexual selection is strong because

relatively few high-quality males will monopolize most of the copulations. Consistent with this, a meta-analysis of data for ungulates provided support for the Trivers-Willard hypothesis [57]. Complications arise when daughters "inherit' their mother's social rank or adult daughters compete with their mothers for local resources, as is the case with some primates and marsupials [45,73,74]. When this occurs, females of high rank can produce more daughters whereas females of low rank can produce more sons especially when competition for resources is high [58]. In primates, a meta-analysis shows that subordinate individuals produce more cortisol than dominants [75], although this negative relationship between social status and GC production might not be necessarily true for all mammalian species [76]. Hence, the diversity of associations between maternal social status and offspring sex may contribute to the differences in the sense of the effect of maternal GCs on offspring sex ratio in mammals.

There is also variability in the directional patterns of the stress-induced effects on sex ratio of birds, which may partially be explained by the different types of relationships between mate attractiveness and relative fitness of sons and daughters. In birds, more than 90% of all species are socially monogamous. Mate choice is constrained by the availability of unpaired individuals in the population and having an unattractive mate can be stressful for the female [77–79]. The mate attractiveness hypothesis predicts that females mated to unattractive males should produce more daughters because these daughters will not inherit their father's unelaborated sexual ornaments [80]. However, the reverse prediction exists in Gouldian finches and maybe other, similar species because of the higher mortality for daughters than for sons of genetically incompatible pairs [81]. In both Gouldian and zebra finches, females with elevated corticosterone levels produce more male offspring [29,30]. It is assumed that such manipulation is under female control, because female birds are the heterogametic sex (Box 2). In species in which males are the heterogametic sex, fathers may

play a role in controlling the sex of offspring. Recent advances in mammals shows that the proportion of X- and Y-chromosome bearing sperm can vary between individuals, reinforcing the need to consider paternal characteristics, including stress, in future studies ([82,83], see Outstanding questions).

Predation and sex-biased dispersal

Sex-ratio adjustments in response to stress might be especially important in situations where predation is the main stressor since it is a major evolutionary force acting on prey and changes in predation risk tend to occur slowly rather than varying greatly from one year to the next [84]. Individuals within the same population can be exposed to varying degrees of risk. For instance, young are generally more vulnerable to predation, but their probability of being predated upon sometimes depends on body condition [85]. For individuals subjected to high predation risk, escaping through a higher dispersal potential might constitute an optimal strategy to increase the probability of survival. In this sense, offspring common lizards (*Zootoca vivipara*) whose mothers were exposed to predator cues disperse three times further than those of non-exposed mothers [86]. Alternatively, one could argue that philopatry would instead increase in offspring of stressed females, as demonstrated in common lizards artificially exposed to GCs [87]. In either case, it is possible that the sex with the highest probability of survival (by staying or migrating more than the other sex) in a dangerous environment would be overproduced. In lizards and fish, there is no clear general pattern of sex-biased dispersal, although juvenile males have been reported to disperse more in some lizards [88] and migrating fish (*e.g. Oncorhynchus mykiss* [89]). The picture is clearer for mammals in which males generally (but not always) disperse more than females, while the reverse is typically observed in birds [90,91]. Hence, if we consider that high dispersal potential is somehow related to differential survival between sexes under high predation, then

more males should be produced in the majority of mammals, while more females should be produced in most birds. Studies combining measurements of predation risk, sex ratio and GC levels are now needed to test these predictions.

Concluding Remarks

The sensitivity of the sex ratio to GC levels appears very variable among vertebrates. The effects are more prevalent in fish and birds than in reptiles and mammals. The different mechanisms of sex determination (genetic vs. environmental) are not sufficient to explain these results because GSD is found in birds and ESD occurs in many species of reptiles. Stress-related sex ratio biases are not necessarily more extreme in fish, but the direction of the sex-ratio skew is uniform in comparison with the other taxa. While it is possible to propose an adaptive explanation for most of these trends, more studies are necessary to test them in a comprehensive meta-analysis. Fitness functions are essential for understanding the adaptive significance of stress-related sex-ratio bias and there are obvious benefits to conducting such investigations in the wild. A better knowledge of the physiological mechanisms that link maternal and environmental stressors to offspring, by taking advantage of both new non-invasive tools (Box 1) and useful animal models, would also be particularly helpful for an integrative understanding of stress-related sex ratio variation (see Outstanding questions).

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Box 1: Stress and glucocorticoids

A widely used definition of "stress" is "the physiological cascade of events that occurs when

the organism is attempting to resist death or reestablish homeostatic norms in the face of insult" [2]. The secretion and synthesis of glucocorticoids (GCs) is considered the primary endocrine response (together with the release of catecholamines) to unpredictable or uncontrollable stimuli (stressors) in the environment [92]. In the wild, high GC levels could result from many different types of stressors including predator attack or presence [93], high population density [94], habitat degradation [95], food shortages [96], social conflict [97] or human activities [98]. Here we considered all GCs increase resulting from these stressful cases, although it is worth noting that harsh conditions do not necessarily provoke a stress response [76].

Stressors can be classified as **acute** or **chronic**, with acute being of short duration (minutes to hours) and chronic being days to months [84]. Some acute stressors can, however, have long-lasting consequences. The effects of stress may even span generations. These transgenerational effects are often due to the transfer of GCs from the mother to the progeny, through eggs in fish [99], birds [100] and reptiles [101] or blood and milk in mammals [102].

The reliability of GCs to assess chronic stress has recently been questioned [103]. Indeed, animals can show unchanged or lower GC levels after exposure to chronic stress [103]. Some of this ambiguity may be due techniques used to quantify GC levels and habituation to the chronic stress methodology in the laboratory studies [104]. Although blood sampling has been commonly used for measuring GC concentrations, it is not necessary the most pertinent method [105]. Integrated and non-invasive measure of GCs, such as those from feces, hair, scales, feathers, surrounding water, may more reflect the cumulative exposure of individuals to GCs rather than repeated measurements of GCs in blood or saliva [104–107]. The evaluation of several stress response parameters remains strongly recommended for a correct interpretation of data [106].

Box 2: How GCs interact with sex determination and sex differentiation

Gonadal sex determination refers to "the decision to differentiate as a testis or an ovary" [1], so that sex determination occurs chronologically before sex differentiation and GCs could interfere with both processes. For instance, in avian species, corticosterone may influence sex-chromosome segregation at the first meiotic division, thereby acting directly on sex determination. This is possible because, in birds, females are the **heterogametic sex** (ZW chromosomes) and have therefore a high degree of control over the sex ratio of the offspring they produce (Figure I). In mammals, morphological differences between X-chromosome-bearing (X-CBS) and Y-chromosome-bearing sperm (Y-CBS) have been found. X-CBS are larger than Y-CBS because they contain more DNA and these two kinds of spermatozoa can have differential survival rates both before and after ejaculation (*i.e.* in the female reproductive tract) [82]. Stress might directly alter the female physiology, making sperm survival sex chromosome specific [34]. There is also evidence that the oocyte susceptibility to X-CBS or Y-CBS can vary according the stress of the female [108].

Furthermore, phenotype and genotype are not always aligned. A potential well-conserved mechanism involves control of aromatase (enzyme converting androgens into estrogens). In fish, as in reptiles, aromatase is central to determining the sexual fate of ambisexual gonads [51,109]. This enzyme could be controlled by GCs, as demonstrated in the Japanese flounder where complex cortisol/glucocorticoid receptors (GR) bind to the glucocorticoid response element (GRE) on the aromatase promoter to decrease aromatase expression, resulting in an overproduction of males [6] (Figure I). Surprisingly this interaction between GCs/GR/aromatase appears to be well conserved in human testicular Leydig cell tumors, also triggering a decrease in estrogen production [110]. In a normal functioning, the appropriate intrauterine sexual steroid balance is also fundamental in humans, since female differentiation (occurring from 7 to 12 weeks post conception) is vulnerable to androgen before the

protective placental aromatase appears [111]. During this sex differentiation period, standard cortisol production reduces androgen synthesis, allowing normal female sex differentiation [111]. Remarkably, in humans, mutations in the cortisol synthesis pathway, decreasing cortisol production, is involved in the virilization of 46, XX girls with congenital adrenal hyperplasia [112]. Cortisol thus appears to plays a key role in different species concerning the balance of sexual steroids. The extent to which stress-linked cortisol production would affect human and other animals sex differentiation, remains an open question. We nevertheless recommend systematically investigating the genotypic sex of focal species to detect for potential stress-induced sex reversal.

Figure I An overview of mechanisms by which glucocorticoids (GCs) can influence sex determination and sex differentiation in vertebrates. X-CBS: X-chromosome-bearing sperm; Y-CBS: Y-chromosome-bearing sperm.

Glossary

Acute stressor: short-term environmental challenges to the physiology of the animal.

Chronic stressor: long-term environmental challenges to the physiology of the animal.

Cortisol: The main glucocorticoid hormone produced by fish and most mammals through the hypothalamic-pituitary-adrenocortical (Interrenal for fish) axis, and released in response to stressors.

Corticosterone: The main glucocorticoid hormone produced by birds, reptiles and amphibians and released in response to stressors.

Environmental sex determination (ESD): sex is determined by external factors, such as temperature, water (pH, oxygen), or density of conspecifics.

External predictive adaptive response (PAR): a form of developmental plasticity in response to environmental cues acting early in life, but where the advantages of the induced phenotype manifest only later in life.

Genetic sex determination (GSD): sex is determined by the presence or absence of genes, generally located on sex chromosomes.

Glucocorticoids (GCs): a class of steroid hormones present in all vertebrates, involved in many physiological processes such as response to stress.

Heterogametic sex: the sex that has two different sex chromosomes (male XY in mammals; female ZW in birds).

Homogametic sex: the sex that has two identical sex chromosomes (female XX in mammals; male ZZ in birds).

Primary sex ratio (PSR): initial sex ratio when sexual differentiation occurs.

Offspring sex ratio: proportion of offspring that are males at different scopes (species, population, individual, clutch/litter). Here, sex-ratio is generally considered at the clutch/litter level.

Secondary sex ratio (SSR): sex ratio after sex differentiation that results from potential sex-specific mortality before birth.

Sex determination: any of the various mechanisms in which the sex of the individual animal is determined.

Sex differentiation: The process following sex determination, where the development of a undifferentiated primordial gonad into testes or ovaries occurs.

Figure Caption.

Figure 1. Effects of glucocorticoids (GCs) on the sex ratio of different species of fish, reptiles, birds and mammals (animal design: Pierre Lopez). Glucocorticoids were applied or measured: before conception; around sex determination or differentiation; during the late phase of gestation or development. Highs levels of stress can induce increases in the proportion of males (animals in blue), reductions in the proportion of males (animals in red) or no change at all (animals in grey). GCs were measured in the mother for all mammals and birds (except 34), while for fish and most reptiles (except 23; 24) it was measured on the animal itself. Number in bracket indicates the corresponding reference. Full black circles indicate species for which primary sex ratio was assessed, while empty circles indicate species for which secondary sex ratio was determined. Note that for the two marsupial species (42,47) the exact timing of GCs measurement relative to pouch status is unknown due to its particular development.* Caimans were exposed to a temperature protocol producing 100% males and exposure to GC did not change this pattern.

Figure 2. The pattern of fitness that can be observed if the sex-ratio adjustments in response to stress are adaptive. The three panels represent adaptive scenarios because the lines cross. Sex A can be either male or female. The sex that gains the greater fitness benefits in a hazardous environment (sex A) should be preferred under high stress conditions, and the other sex (sex B) should be preferred under low stress conditions.

Figure 3 Duration of incubation or gestation time (days) as a potential driver of sex-ratio adjustments in response to stress in teleost fish (n=53), birds (n= 447), reptiles (n=7) and

mammals (n=420). Box plots show the mean represented by black diamond, the median represented by lines, first and third quartiles as well as outliers represented by full circles outside the box. Note that 14 outliers > 400 days were omited in mammals for design purpose. Signs and background color represent the strength of the match between the environment experienced at the time of sex determination (SD) and the one experienced by newly born offspring, with "+" indicating a strong match and "-" indicating a weak match. The dashed line represents the average SD for most represented species (note that it could occur during incubation or later for some fish and reptiles). Data were extracted from the dynamic energetic budget website (https://www.bio.vu.nl/thb/deb/) reporting the life history traits of more than 1500 species.

Highlights

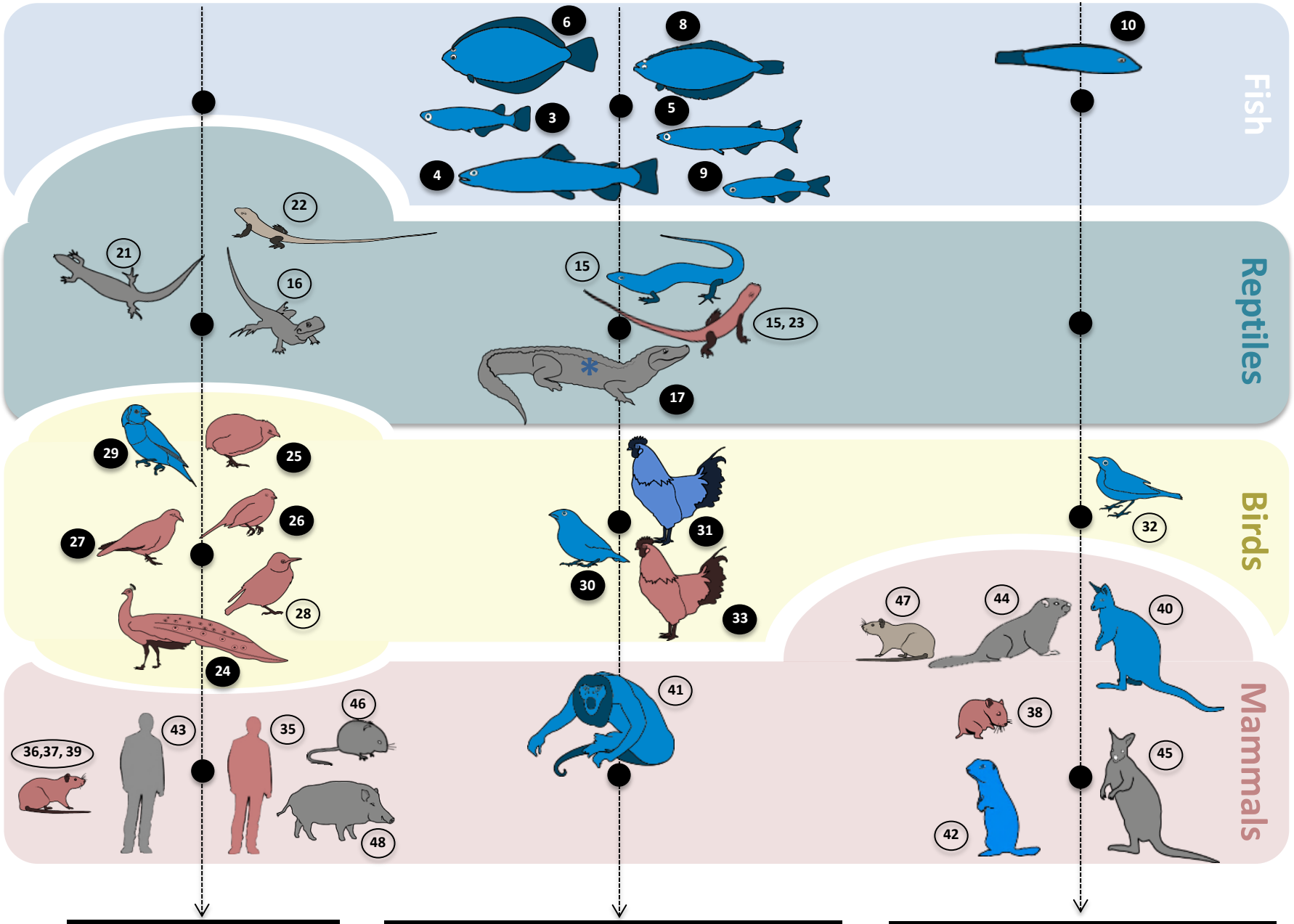
- Offspring sex ratios have been shown to correlate with environmental stressors and maternal stress in many vertebrate species.
- There is an adaptive advantage for parents to produce the sex that is more likely to survive and reproduce in a future hazardous environment.
- In the fastest life histories, there is more likely to be a close good match between the environment around sex determination and the offspring's future environment.
- Glucocorticoids are key messengers of environmental contexts that likely influence the sex determination processes of various species.
- A combination of field and laboratory studies is required to understand the extent to which stress influences offspring sex from conception to birth.

OUTSTANDING QUESTIONS:

Although we have demonstrated that there is a relationship between stress and sex ratio and

that this varies strongly between vertebrates, many areas are still little understood. Questions for the future include:

- Do chronic and acute increases in GCs act on sex determination through similar mechanisms?
- Do increases in GCs during the sex differentiation period in reptiles change the sex ratio?
- To what extent could sexual dimorphism in other life history traits such as age at maturation, growth or metabolism drive the production of a certain sex under stressful conditions?
- To what extent key life history traits, allowing to distinct fast and slow selected species, explain the sensitivity of offspring's sex to stress?
- Does paternal stress explain sex ratio skews that are not explained by maternal stress in species, such as mammals; where males are the heterogametic sex?
- Are sex ratio skews the product of differences in the susceptibility of the two sexes to environmental stressors or are they the consequence of adaptive adjustment by parents?
- Does the presence of the chorion, which potentially protects the embryo during initial phase of sex differentiation mechanisms from external stressors, increase selection for a master sex determining genes in some fish species?
- Is the differential mortality between sexes linked with stress at the earliest stages of development?
- To what extent are epigenetic mechanisms and stress-related information linked?
- Do GCs act alone to skew sex ratios or in combination with other non-sexual steroid molecules such as glucose?


Fish
Reptiles
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42
Before Conception
Around sex determination or sex differentiation
Later in gestation or development

Without Stress

With Stress

Gamete Level

50% 50%

WZ ZZ

50% 50%

XY XX

Hormonal Level

Gene Enzyme Hormones Organs

aromatase

GRE

Estrogens +

Aromatase

Ovaries

Androgens

Testes

X X

X Y

Sex determination

Sex differentiation

WZ

Sex chromosome meiotic drive

X Y

Differential susceptibility of the oocyte to X-CBS and Y-CBS

Differential survival of X-CBS and Y-CBS in the female reproductive tract

GR

GRE

aromatase

Estrogens -

Ovaries

Aromatase

Androgens +

Testes

Control of the aromatase by GCs

X X

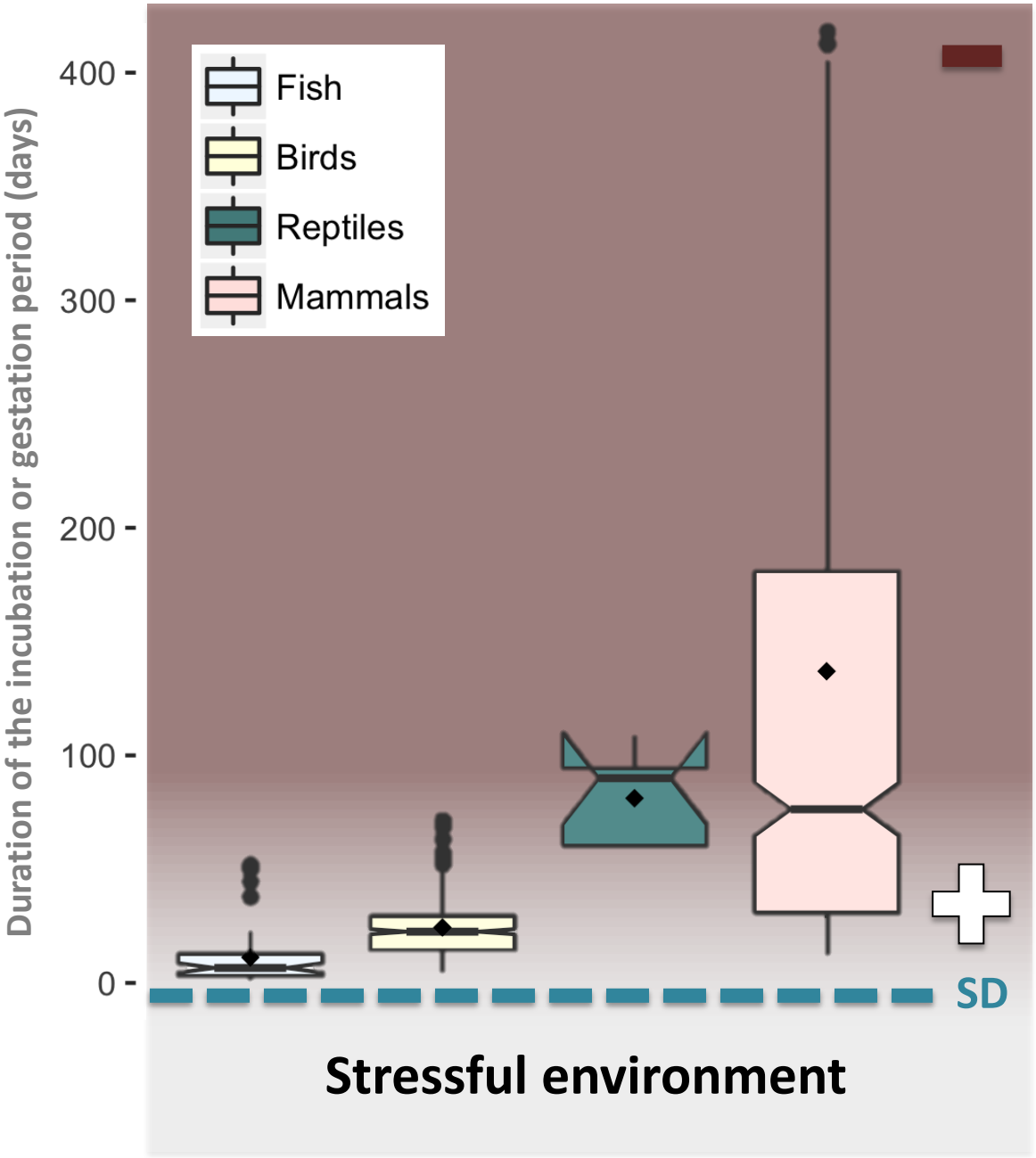
Y dead

dead dead

X X

X Y

Sex-specific mortality early in gestation/incubation


Fish
Birds
Reptiles
Mammals
400
300
200
100
0
Duration of the incubation or gestation period (days)
SD
Stressful environment