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Does the interaction between glucocorticoids and insulin-like growth factor 1 predict nestling fitness in a wild passerine?

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ABSTRACT

The crucial question in evolutionary ecology is to find out how physiological traits have coevolved so animals fit their stochastic environments. The plasticity of these different physiological mechanisms is largely mediated by hormones, like glucocorticoids and insulin-like growth factor 1 (IGF-1). Brood size manipulation with nestlings of free-living great tits (*Parus major*) was carried out to see the way in which plasma IGF-1 and feather corticosterone, a predictor of long-term sustained plasma corticosterone level, are associated across different nutritional conditions and how this association predicts survival during the nestling phase. We showed that the association between levels of IGF-1 and corticosterone depended on physiological condition of nestlings. Namely, there was a positive association between the hormones in nestlings from the decreased broods and a negative association in nestlings from the enlarged broods. Furthermore, we showed that the interaction between levels of IGF-1 and corticosterone was also related with the survival of the nestlings. Our results suggest that signalling pathways of IGF-1 and corticosterone most likely interact with each other in a nutrition-dependent way to maximize the rate of development and survival of nestlings in their stochastic environment.

1. Introduction

Nutrition is among the principle selective forces shaping fitness-related traits like physiological condition and survival of animals during early postnatal development. A complex combination of various hormone signalling pathways offers an underlying physiological mechanism for this life-history variation. Central to this phenomenon are the growth hormone (GH)/insulin-like growth factor (IGF) and the hypothalamic–pituitary–adrenal (HPA) axes that regulate the attainment of normal growth, physiological condition and survival in vertebrates by altering gene transcription and protein synthesis of various signalling pathways (Dufty et al., 2002; Lupu et al., 2001; Nanto-Salonen et al., 1993; Sapolsky et al., 2000; Stratikopoulos et al., 2008). However, the physiological interaction between those hormones has not been studied to date on free-living animals.

Insulin-like growth factor 1 (IGF-1) is synthesized mainly in the liver as the end product of the GH/IGF axis (Lupu et al., 2001). IGF-1 has an essential role in stimulating cell proliferation and differentiation, for example in bone and muscle tissues (Otto and Patel, 2010; Yakar et al., 2002). Biological activities of IGFs are modulated by a set of specific IGF-binding proteins (IGFBPs), and are mediated by specific receptors on the cell surface even in various parts of the brain and spinal cord (Bondy and Cheng, 2004; Hwa et al., 1999; O'Kusky et al., 2000).

Glucocorticoids are steroid hormones, secreted into the bloodstream by the adrenal glands via the HPA axis in response to various environmental signals (Charmandari et al., 2005; Sapolsky et al., 2000). At low levels, physiological effects of glucocorticoids on somatic growth tend to be stimulatory, while becoming predominantly inhibitory as concentrations increase (Sapolsky et al., 2000). In medical literature it is relatively well characterized that glucocorticoids promote the gene expression pattern needed for normal osteoblast development (Bellows et al., 1987) and increase dysferlin expression needed for myogenesis (Belanto et al., 2010). As glucocorticoid levels increase to overcome environmental challenges, their physiological effects tend to retard somatic growth to invest more in short term survival (Lodjak et al., 2015; Sapolsky et al., 2000).

An important mechanism that affects overall fitness of an individual vertebrate through selective resource allocation between different physiological functions involves the interaction between glucocorticoids and IGF-1. At relatively low plasma levels, glucocorticoids mediate the maturation of the GH/IGF axis during prenatal development in chickens (Bossis and Porter, 2003; Zheng et al., 2008). Furthermore, it has been shown that glucocorticoids are needed for growth hormone synthesis, and when thyroid

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hormones are present, this physiological effect is even more pronounced (Martial et al., 1977; Mazziotti and Giustina, 2013). On the other hand, when environmental challenges for animals increase, high glucocorticoid levels start to inhibit costly investment into the GH/IGF axis. For example, in the tilapia (*Oreochromis mossambicus*), administration of a relatively high dose of exogenous cortisol (main glucocorticoid in fish) significantly decreased plasma IGF-1 levels in the blood and IGF-1 mRNA expression in the liver (Kajimura et al., 2003), suggesting that a decrease in plasma IGF-1 levels is mediated through the attenuation of IGF-1 gene expression. This change, in turn, can be mediated by glucocorticoid-induced inhibition of growth hormone or its receptor synthesis as shown in humans and rats (McCarthy et al., 1990; Unterman et al., 1993). Interestingly, to some extent IGF-1 can modulate the physiological effect of glucocorticoids, mainly through peripheral metabolism. For example, IGF-1 inhibits the expression of 11β-hydroxysteroid dehydrogenase 1 and enhances the expression of 11β-hydroxysteroid dehydrogenase 2 in the adipose tissue and liver, which means that the local conversion of glucocorticoids from an inactive to active form is decreased and the clearance rate of the hormone from the bloodstream is increased (Paulsen et al., 2006). It has also been shown that IGF-1 acts as a reparatory mechanism for tissue damage inflicted by sustained high glucocorticoid levels (Latres et al., 2005; Pansters et al., 2013; Stitt et al., 2004).

Furthermore, studies in humans have shown that nutritional conditions during early postnatal stages of development modulate the developmental rate of individuals through changing the levels of IGF-1 and glucocorticoids (Cianfarani et al., 1998). Primarily, this nutrition-mediated hormonal interaction likely functions via two physiological mechanisms. Firstly, the levels of adipocyte-derived leptin (anorexigenic hormone) and liver-derived ghrelin (orexigenic hormone) are sensitive to the nutritional condition of the organism and likely influence synthetic pathways for glucocorticoids and IGF-1 via the hypothalamus paraventricular nucleus. This likely occurs in a similar way in mammals and birds (Cassy et al., 2003; Inui, 2001; Kaiya et al., 2013; Li et al., 2011). In addition, under food limited conditions, an increased level of ghrelin, which increases the food intake of an individual (Wren et al., 2001), has a direct stimulatory effect on the secretion of GH (Kaiya et al., 2013; Takaya et al., 2000). It is important to note that IGF-1 secretion in response to GH is likely initiated, only when the nutritional compounds are present. Secondly, the activation of the IGF-1 initiated growth promoting phosphatidylinositol-3 kinase/protein kinase-B/mammalian target of rapamycin (PI3K/AKT/TOR) signalling pathway needs additional signals from nutritional compounds (e.g. amino acid), whereas it is inhibited in conditions where food is a limiting factor (Fingar and Blenis, 2004).

In wild birds, we have previously shown that IGF-1 levels measured from plasma (Lodjak et al., 2014) and corticosterone (main avian glucocorticoid) levels measured from feathers (Lodjak et al., 2015) are sensitive to growth conditions. Although, to date, the relationships of glucocorticoids with IGF-1 have not been tested in birds, we can expect that this relationship be crucial for determining the plasticity of growth rate in all vertebrate animals, including birds. In this study, brood size manipulation with an altricial free-living passerine bird, the great tit (*Parus major*), was carried out to see the way in which the plasma IGF-1 and feather corticosterone are associated in nestlings during postnatal development under different nutritional conditions. Previous studies on birds have shown that feather corticosterone can be effectively used as a proxy for sustained plasma corticosterone level (Fairhurst et al., 2013; Lodjak et al., 2015). Our hypotheses rely on assumptions that the synthesis of the corticosterone and the IGF-1 are nutrition-dependent and on the fact that their signalling pathways interact with each other at the molecular level (see above). It has been shown that brood size manipulation affects *per capita* food provisioning compared to those in control broods (Pettifor et al., 2001; Sanz and Tinbergen, 1999). Given that nestlings in decreased and enlarged broods are in relatively better and relatively worse conditions respectively, we expected that the association between the plasma IGF-1 and feather corticosterone is sensitive to postnatal growth conditions. Therefore we firstly predicted that the association between the hormones differs between treatment groups and secondly, we expected that the nutrition-dependent inter-regulation of IGF-1 and corticosterone can be linked to short-term fitness, in terms of fledging success, in nestlings.

2. Materials and methods

2.1. Study system

Data were collected from May to June 2012 from a free-living great tit population near Kilingi-Nõmme in south-western Estonia (58°7′N, 25°5′E). The study area, approximately 50 km^2, is covered by a mosaic of deciduous and coniferous forest patches, dominated by grey alder (*Alnus incana*), silver birch (*Betula pendula*) and Scots pine (*Pinus sylvestris*). Nest-boxes, mounted on tree trunks at a height of 1.5–1.8 m, were checked regularly to obtain precise egg laying dates, clutch sizes, hatching dates of the first egg (hatch date = day 0 post-hatch) and brood sizes. The nest boxes had inner dimensions of 11 × 11 × 30 cm (Lambrechts et al., 2010) and the entrance hole diameter was 3.5 cm. All nest-boxes were situated along line transects with an average spacing of 50–60 m. Before the beginning of the breeding season the nest-boxes were either repaired, or replaced with new ones. Subsequently old nest material was removed, therefore the average age of the nest-boxes was expected to be similar between the treatment groups.

2.2. Brood size manipulation and sampling

To experimentally manipulate growth conditions of nestlings, a brood size manipulation was carried out with 2-day-old nestlings. Broods with the same hatching dates were randomly assigned to one of three treatment groups: decreased, control or enlarged broods. Two randomly selected nestlings from the decreased broods were relocated to corresponding nests in the enlarged group. Nestlings from the control group were handled in the same way, but they were returned to their own nests. Mean (±SD) manipulated brood sizes were 8.91 (1.44) for decreased, 11.25 (0.97) for control, and 12.35 (1.93) for enlarged groups. The mean laying date ($F_{2,56} = 0.21$, $p = 0.81$) and clutch size ($F_{2,56} = 0.76$, $p = 0.47$) did not differ between the treatment groups. On day 15 post-hatch blood samples (~70 μl) were obtained from the brachial vein to measure plasma IGF-1, and two tail feathers (the outermost feather from each side) from three randomly selected nestlings per brood were obtained, to measure corticosterone levels. No adverse physiological effects on nestlings were noted due to the sampling procedure.

2.3. Hormone analysis

Corticosterone was measured from feathers, which were minced into small pieces (<5 mm^2) and subjected to methanol based hormonal extraction. The supernatant was then measured using a radioimmunoassay approach (RIA). For specific description of methods used, see Lodjak et al. (2015). It is important to note here that the corticosterone measure from feathers is a distinctly different compared to plasma samples, therefore, we remain cautious when linking levels of feather corticosterone with plasma