Integrating Adaptive Trade-offs between Parental Care and Feeding Regulation

Cynthia O'Rourke and Suzy C. P. Renn

Department of Biology Reed College
3203 SE Woodstock Blvd
Portland OR 97202 USA

renns@reed.edu
orourcy@reed.edu

Corresponding Author: S.C.P. Renn

Abstract

Animals respond to external and internal stimuli to decide which behaviors to produce. Only by addressing the mechanistic relationships between the regulation of different behaviors, and by doing so in an ecological context, will we fully understand the decision process. For example, regulatory mechanisms for feeding behavior and those for parental care behavior are studied largely in isolation, though these behaviors are inextricably linked. Understanding this fundamental behavioral trade-off between investment in current and future reproductive output requires an integrative approach. We identify direct cross-talk mechanisms in neuropeptide signaling pathways that regulate both behaviors and indirect cross-talk mechanisms as factors that impinge on critical neuropeptides. Furthermore, external cross-talk exists through behavioral feedback. A deliberately integrative approach is necessary to understand behavioral decisions that are fundamental to predictions of life history theory.

Introduction

Animal behavior is flexible, and the decision regarding which behavior to produce depends on context and situation. To produce behaviors that optimize fitness, the brain must decide or prioritize among potentially conflicting external and internal stimuli in order to activate appropriate neural circuits. Only by addressing the mechanistic relationship between these behaviors is it possible to understand the decision process. However, both empirical and theoretical work often still address such decisions and the production of adaptive behaviors within a single context [1], e.g., studies of either nurturing or foraging rather than simultaneous studies of nurturing and foraging as behaviors that respond to one another. In fact, these behavioral decisions proximately represent trade-offs that affect growth, reproduction, and survivorship (*i.e.* life history traits). Therefore, it is important to integrate ecological/evolutionary approaches related to fitness and functional/mechanistic approaches related to neuroscience. Given recent genomic and molecular advances as well as physiological assays this is now possible in diverse biological systems [2].

The most fundamental life history trade-off lies at the intersection of current versus future reproductive output. Resources that are dedicated to current offspring become unavailable for somatic maintenance or future reproduction. One of the simplest examples of this trade-off is the increased per-event reproductive investment of semelparous versus iteroparous organisms – organisms that reproduce only once versus reproduce more than once over the course of their lifetime. This pattern is demonstrated, for example, by drastic lipid store losses over the course of the mating and parental care season in the semelparous *Etheostoma perlongum* darter fish, relative to moderate lipid losses over the course of the mating and parental care season in the closely-related iteroparous *E. olmstedii*, another darter fish. Inverse correlations between potential number of reproductive events and immediate reproductive investment exist even within species. For example, guppies (*Poecilia reticulata*) exposed to predation pressures that curtail adult lifespan mature earlier and produce more offspring per reproductive event than do guppies exposed to offspring-directed predation pressures that allow for extensive adult lifespans [3,4]. In mammals, lactation costs, particularly when coupled with low food availability, restrict offspring growth rates and negatively impact measures of somatic maintenance such as wound healing time and time between reproductive events [5-7].

For most species, the diverse set of activities that compose “feeding” and “parental care” must be co-regulated through partially overlapping neuroendocrine circuits, and evidence indicates substantial cross-talk between these circuits in at least some species (e.g., [8-10]). The mechanisms governing feeding behaviors and reproductive behaviors have separately garnered substantial investigation, and yet the integration between them remains largely unexamined, particularly in a comparative context that accounts for life history strategy. Given temporal variability of parental demands within an individual’s life span as well as the evolutionary lability of mating system and parental involvement between species, it is critical to ask whether the mechanisms integrating feeding behaviors and parental care behaviors are consistent, or whether they vary temporally within a species as well as between species.

Parental care, an evolutionarily labile trait with substantial implications for fitness, is a major component of animal diversity. While most differences in care between closely related species are in the degree of

investment rather than in the overall form that the care takes, in some clades comprehensive parental care systems have repeatedly emerged and disappeared [11]. Within a species, individuals may plastically adjust their level of investment in response to resource availability, brood size, brood quality, predation threat, paternity assurance, or their partner's level of investment [12]. The prevalence of care-providing species, the evolutionary lability of care systems, and the frequency of investment plasticity together suggest possible evolutionary conservation of the basic neural mechanisms of care across a wide range of vertebrate species which can be understood through a comparative approach. It is worth noting that the functions of several candidate molecules for feeding regulation as well as those for care regulation appear to have diverged between major vertebrate clades. In teleost fishes, furthermore, a genome duplication creates the added complexity of potential subfunctionalization and neofunctionalization in teleost paralogs of mammalian candidate genes. These divergences should be kept in mind when comparing across clades, but are in themselves useful for identifying mechanisms of regulatory cross-talk that have repeatedly evolved in response to a shared evolutionary pressures: the need to balance current reproductive investment with future reproductive potential.

Where does cross-talk occur?

All behaviors are regulated by internal and external stimuli. Behavioral adjustments in either feeding or care are no different. Feeding is regulated by external stimuli related to food availability as well as by satiety, metabolic, or nutritional state. Care behaviors are regulated by external stimuli in the form of social cues from offspring as well as internal stimuli connected with hormonal state. The cross-talk between these regulating mechanisms can occur internally at the mechanistic level or externally at the behavioral level through feedback. Neural signals implicated in both feeding regulation and care regulation have the potential to directly affect the activities of both behaviors, while other signals implicated only in one behavior have the potential to indirectly affect the other by responding to or stimulating release of key signals. Additionally, both feeding and parental care are frequently mediated by the same behavioral stress responses (*e.g.*, glucocorticoids), which can be invoked by the output of either of these behaviors - for example, in response to energy deficits [13] or in response to a perceived threat to the offspring [14]. The regulation of feeding and parental care are therefore linked at different levels of biological organization (Figure 1).

Co-regulation of care and feeding is an under-examined subject, and as a result mechanisms of integration are largely unknown. To identify such mechanisms, the expression of feeding-related and care-related circuits should be studied under various conditions that would necessitate adjustment in the tradeoff. Sites of integration mechanisms would be indicated by changes in care-related circuits under varying conditions related to energy budget such as food availability. Likewise, sites of integration mechanisms could be indicated by changes in feeding-related circuits by varying conditions related to parental care, such as offspring interactions. Experiments should be designed to measure behavioral and physiological effects of these interactions, as well as, changes in gene expression, including *in situ* hybridization to localize changes in receptor expression or regulatory molecules implicated in one behavior in response to changes in the other behavior. RNA-Seq and other discovery-based approaches would be particularly useful given the dearth of solid hypotheses in this nascent field of study and lack of many known candidates for integrating mechanisms. The advent of CRISPR allows for functional testing of integration candidates in non-model organisms; animals with deletions of positive regulators of integration mechanisms should show a reduced ability to adjust feeding behaviors in response to care

conditions, and/or a reduced ability to adjust care behaviors in response to feeding conditions. Alternatively, established pharmaceutical routes of manipulation may reveal regulatory mechanisms by modifying single known regulatory elements of one behavior in order to assess effects on the other behavior. When choosing a methodology and experimental timeline, researchers should keep in mind that regulation and hence regulatory cross-talk may be instantaneous or sustained, depending on the mechanism and species involved. Some sampling protocols and molecular analyses will be appropriate for immediate and transient responses, while other experimental designs will suit delayed and/or sustained responses.

Direct integration of care and feeding regulation

Both feeding and care behaviors in vertebrates are regulated by interplay among the hypothalamus, other brain regions, and peripheral systems [15,16], often orchestrated through conserved hormonal and neuropeptide signals. In mammals, neural circuits undergo dramatic modulation to allow expression of maternal care behaviors, the “maternal brain” (e.g., [17]). The maternal brain, as described in mammals, includes molecular, cellular, and hormonal changes occurring within a well-defined and conserved anatomical network of brain nuclei. The most well-studied and dramatic transition occurs at parturition, when the hormonally primed medial preoptic area (mPOA) responds to offspring by initiating two cascades via different neural circuits [18], first, inhibiting the withdrawal from offspring, and second, activating the dopamine reward system to promote pro-maternal care. Similarly, there is a well-defined regulatory circuit for feeding. The arcuate nucleus of the hypothalamus contains two specific populations of neurons, one producing the appetite-promoting or “orexigenic” signals neuropeptide Y (NPY) and agouti-related peptide (AgRP), and the other producing the appetite-suppressing or “anorexigenic” signals pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). These cell populations are directly responsive to the peripheral signals of satiety, such as leptin, and of hunger, such as ghrelin [19]. Several nuclei of the maternal brain receive direct input from the feeding regulatory neurons of the hypothalamic arcuate nucleus [20].

Perhaps the best-studied direct interaction between care and feeding regulation involves prolactin signaling in mammals. Among its many documented functions, the neurohormone prolactin has been implicated in the promotion of parental care activities in both females and males (fish: [21]; mice: [22]), including avian crop milk secretion (chickens: [23]), teleost epidermal mucus secretion (discus fish: [24]), and offspring grooming and attendance (new world monkeys: [25]). A role for prolactin in feeding regulation has been documented in birds, where it is known to drive increases in AgRP secretion during late-stage parental care (ring doves: [26]). Similarly, prolactin has been shown to lead to decreased sensitivity to anorexigenic α -melanocyte-stimulating hormone (α -MSH, a derivative of POMC) in lactating mammals [27].

These mechanisms of direct integration allow intricate links in behavioral regulation as predicted by life history theory [28]. Caring parents must maximize energy intake around the complications of care schedules both to provide for current offspring and to reserve energy for future reproductive opportunities. These behaviors result in myriad peripheral feedback signals integrated by the brain. For example, in addition to regulating feeding behavior in response to peripheral leptin and ghrelin, the

arcuate nucleus is also a key site for integration, receiving serotonergic input [19] as well as GABAergic and glutamatergic inputs [29] from diverse brain regions, allowing for complex cross talk.

Indirect integration of care and feeding regulation

The indirect interactions of feeding and care regulatory mechanisms involve factors that impinge on shared signaling systems. Several gene products either up- or down-regulate care-related prolactin expression and also affect feeding behaviors - for example, somatostatin, several endocannabinoids, and α -MSH [30]. The pro-appetitive hormone ghrelin is a particularly interesting candidate, as it stimulates prolactin secretion in fishes, frogs, and humans, and is up-regulated in lactating mammals [31,32]. Ghrelin does not, however, stimulate prolactin secretion in humans with the appetitive disorder anorexia nervosa [33], indicating overlap between care and feeding regulatory circuits in humans, with ghrelin at or upstream of that integrative mechanism. The satiety hormone leptin is another strong integration candidate. Binding of leptin to receptors in the arcuate nucleus increases food intake in mammals [34]. Leptin signaling is negatively regulated by parental care in both male prairie voles and lactating female mice. Interestingly, in voles paternal care is associated with lower plasma leptin levels, while in mice maternal lactation is associated with resistance to leptin with normal circulating levels [35,36]. Further integration may occur via the positive regulator of male and female parental care, galanin, which is downstream of the leptin anorexic pathway [37,38]. This suggests that there are additional regulatory mechanisms for galanin depending on parental state. For all candidate neuropeptides and hormones, differential receptor expression at specific points along the hypothalamic-pituitary-adrenal axis likely play a role in this regulation.

In addition to regulation by orexigenic ghrelin and anorexigenic leptin [39,40], pituitary release of prolactin can be regulated by serotonin, dopamine, and other prolactin releasing factors [41]. The influence of dopamine occurs both independently and as the result of a prolactin-incorporating negative feedback loop that inhibits prolactin secretion [42-44]. There are positive correlations between dopamine expression levels and both appetite and care within some brain regions [45], and negative correlations between dopamine levels and care within other brain regions [46]. In many cases these site-specific effects depend on hormonal priming of brain nuclei targets [47].

Increases in prolactin secretion and increases and decreases in circulating ghrelin and leptin levels are features of the maternal brain [15]. Pituitary prolactin secretion can be stimulated by prolactin-releasing peptide (PrRP), which induces the hypothalamic release of oxytocin (OT) and arginine vasopressin (AVP) [48-50], two nonapeptide hormones broadly implicated in parental care in mammals [51-54]. OT and AVP also have demonstrated appetite-suppressant effects, but the hyperphagia of lactating mammals and receptor studies suggest a reduction of oxytocin's potential to regulate appetite in lactating mammals [55,56]. In part, this homeostasis is also maintained by suckling-induced increases in orexigenic NPY and AgRP [27,57,58]. The effects of AVP on appetite are less well-studied, but may also be modified by parental care periods. In non-mammalian vertebrates the OT and AVP homologues isotocin and arginine vasotocin have largely been studied with relation to parental care and social behavior [14,59] with fewer studies investigating a role in feeding regulation [60].

Behavioral feedback integration of care and feeding regulation

The energetic outcomes of either feeding or care behaviors may serve as positive or negative regulators of each other (figure 1). Stress and energy deficits, such as those that can result from a reallocation of foraging time to care time, are known to cause a drop in plasma levels of care-promoting prolactin in birds [61]. Life history theory would predict a dampening of prolactin stress response in species for which current offspring are relatively difficult to replace with future offspring. In support of this “brood value hypothesis,” prolactin levels have been found to be less sensitive to stress in species that have fewer reproductive opportunities or greater initial reproductive investment by the care-giving individual than in species with more reproductive opportunities, indicating that increased brood value can select for a decreased prolactin stress response and therefore a decreased response to the energetic consequences of providing parental care [62]. Similarly, mammalian parental plasma prolactin levels tend to remain constant in the face of energy deficits and other sources of stress, such as may result from provisioning and defending offspring. This reduced prolactin response may result from reduced parental sensitivity to some stressors, and from the de-coupling of prolactin’s involvement with care production and with stress response (e.g., [63,64]).

A similar stress response in teleosts is suggested to be mediated by serotonin, which is known to regulate the release of prolactin in many vertebrates [42,65,66]. The serotonin reuptake inhibitor fluoxetine interferes with parental care and induces filial cannibalism in male bettas, an extreme form of resource reclamation. Interestingly, fluoxetine does not interfere with courtship or territorial aggression in the absence of a brood [67], supporting a role linking the regulation of care and feeding behaviors, such that care behaviors act to suppress feeding behaviors in this fish. A divergence from normal prolactin profiles in response to fluoxetine suggests that serotonin is acting indirectly through prolactin signaling [68]. Additional studies are needed to elucidate the mechanisms through which behavioral outcomes feedback to act as stimuli integrating these systems of regulation.

Mechanisms integrating the regulation of feeding and care in invertebrates

For a broad perspective on the evolutionary tradeoffs between care and feeding behaviors, these same issues should be addressed in invertebrates. Many eusocial invertebrate species engage in an exaggerated behavioral switch in which some adult individuals are entirely dedicated to care while others are entirely dedicated to foraging. While little is known regarding the regulatory mechanisms of invertebrate parental care [11], current studies suggest that hormonal mechanisms link neural regulatory pathways. In the holometabolic insects, juvenile hormone (JH) has been broadly implicated in both care behaviors (caste determination: [69]; care quality: [70]) and the cessation of feeding between larval and adult stages [71]. In honey bees JH interacts with vitellogenin, a molecular indicator of food availability, to control transitions between nursing and foraging worker phenotypes [72,73]. This interaction between JH and vitellogenin may have been co-opted from the ancestral solitary maternal transition between nectar feeding and pollen feeding [73], a hypothesis supported by evidence from earwigs revealing the interaction of vitellogenin and JH during the transition between feeding/ovulating to fasting/caring states [74]. That JH alone appears to be a major driver of parental care in the biparental burying beetle [70,75] demonstrates the need for further investigation in the evolution of signals such as vitellogenin, JH, and other juvenoids that may integrate the regulation of care and feeding to mediate behavioral decisions that are critical to the evolution of life history traits. Nonetheless, these invertebrate studies suggest broad analogies between the role of JH regulating

behavioral switches associated with caste- or age-related polyethism involving care phenotypes in invertebrates, and the effects of prolactin regulating repeated transitions between care and feeding in birds [61].

Conclusions

The direct and indirect integration between care and feeding regulation in vertebrates is clear, as is the existence of reciprocal regulation between these two behaviors. How that regulation has evolved as parental care systems have evolved, and to what extent it has been preserved across the animal kingdom through losses and gains of care, remain open questions that can be addressed by more explicit tests of the interaction of these two systems in a broad array of both clades and care systems, at scales spanning gene expression to ecology. Life history theory would predict a greater impact of parental state on feeding motivation when offspring are difficult to replace. This hypothesis has been supported in birds [62] and is ripe for testing in teleost fishes and mammals. Conversely, care should have less of a suppressive effect on paternal appetite when paternity is questionable and less of a suppressive effect on the appetite of either parent in cases of nest parasitism, two hypotheses suited to testing in birds and teleosts [76]. In humans, the causes and mechanisms of post-partum depression (PPD) may involve resource reallocation and co-regulation of care and feeding pathways, as both social environment and appetite dysregulation are associated with PPD [77,78]. Rodent studies suggest that this may be a conserved mammalian trade-off [79], thus demonstrating the relevance of comparative approach to biomedical studies. Immense bodies of ecological and neurological research already exist for mammals, birds, and teleosts, laying the foundation for integrative work testing hypotheses generated from both life history theory and our current knowledge of the molecular mechanisms of care and feeding behaviors. Ecological context provides theoretical explanations for why a behavior “should be,” and neurobiology suggests mechanisms and constraints for how that behavior “can be.” By devising studies that take both fields of research and methodologies into consideration, we can formulate hypotheses and develop models that are far more comprehensive than would be possible when considering, in isolation, only the natural history or only the neurobiology of the organism. In other clades, such as invertebrates, reptiles, and amphibians, basic research into the molecular mechanisms of either care or feeding is independently lacking, but the results of mammalian, teleost, and avian work can generate predictions and inform experimental approaches in these under-examined study systems. Applying what we’ve learned of care and feeding regulation to the deliberate study of the interaction between these behaviors in species representing a range of post-natal investment levels, parental care systems (paternal, maternal, biparental, alloparental, eusocial), and phylogenetic distances can help us to better understand one of the most fundamental predictions of life history theory: that selection will calibrate an animal’s current reproductive investment against its future reproductive potential in order to maximize lifetime reproductive success.

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Figure 1. Regulatory Cross-talk. Cross-talk between the regulatory mechanisms of care behaviors (black lines) and the regulatory mechanisms of feeding behaviors (grey lines) and can occur directly (A) and indirectly (B) and may be co-regulated across a range of physiological scales. Furthermore, the outputs of one behavior often serve as excitatory (C) or inhibitory (D) stimuli for the reciprocal behavior. The extensive cross talk between the regulatory pathways for behaviors necessitates an integrative approach to understand behavioral decisions.

Figure 1