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«Review»

Function of Amino Acids and Neuropeptides in Feeding Behavior in Chicks

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Regulation of food intake, especially during the neonatal period, is important to ensure optimal nutrition and meet the metabolic requirements of growing and healthy animals. However, many problems associated with neonatal chicks remain unsolved. Feeding behavior during the neonatal stage is characterized by short resting periods between very brief times spent taking up food. Accordingly, neuropeptides, which take time to synthesize and release, as well as nutrients that are taken up via feeding, may be involved in feeding regulation. The present review summarizes current knowledge about the role of amino acids and their interaction with neuropeptides on the regulation of food intake in neonatal chicks with special emphasis on L-arginine metabolism and neuropeptide Y. Fasting and subsequent short-term refeeding influence amino acid metabolism in the brain. Short-term refeeding induces a rapid increase in the concentrations of several amino acids, which may contribute to satiety signals in the neonatal chick brain. The function of L-arginine is related to its metabolite, L-ornithine, which acts as an innate satiety signal in the control of food intake. Co-injection with L-ornithine attenuates the orexigenic effect of neuropeptide Y in a dose-dependent manner. This implies a potent interaction in the brain between the regulation of food intake by neuropeptide Y and acute satiety signals by L-ornithine. The roles of other amino acids in feeding and their relationship with the stress response are also discussed in this review. In conclusion, endogenous neuropeptides and endogenous and/or exogenous nutrients such as amino acids are believed to coordinate the feeding behavior of neonatal chicks.

Key words: amino acid, neuropeptide, neonatal chick, feeding behavior, central nervous system

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Introduction

Controlling food intake is crucial for animals, as it allows them to match nutrient availability with their metabolic needs. Understanding the feeding regulatory mechanism is particularly important in juveniles, owing to its influence on animal growth and health. Considerable knowledge on the control of food intake has been gained from studies using mammalian animal models[1–4]. Nevertheless, studying feeding behavior at an early stage of life in rodents is difficult because of insufficient brain size for substance administration and total dependence on parents for feeding. On the other hand, Burt et al.[5] reported that organization of the human genome was closer to that of chickens than the mouse one.

Chicks demonstrate well-developed feeding behavior in the neonatal period. Domesticated chicks are a precocial nestling species, capable of searching for their own food immediately after hatching[6]. Furthermore, neonatal chicks have relatively large brains; hence, the central administration of drugs makes it easy to monitor changes in food intake. According to Davis et al.[7], intracerebroventricular (ICV) injection in neonatal chicks is simpler and more convenient than operating a guide cannula. ICV does not cause stress[8], nor does it affect food intake[9]. Intense genetic selection has resulted in two types of chicks, broilers and layers, for the production of meat and eggs, respectively, with different mechanisms regulating food intake. Broiler chicks develop hyperphagia, with increased food intake and body fat deposition, which may model certain forms of obesity. Therefore, use of neonatal chicks as animal models of food intake regulation may be beneficial for poultry production in terms of appropriate feeding adjustments, but it may also provide insights into feeding behavior across species.

Studies on neuropeptide regulators of feeding in neonatal chicks have revealed fewer orexigenic than anorexigenic candidates, even at an early growth stage[6]. Given that the use neuro-

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peptides as ligands for stimulation, release, synthesis, and storage requires some time, the short feeding interval and overall behavior in neonatal chicks may not be explained by neuropeptides alone. The central sedative, hypnotic, and excitatory functions of amino acids and their metabolites have been widely investigated in neonatal chicks[10], implying a key effect of free amino acids in the brain on feeding behavior. The present review outlines the precise feeding behavior of neonatal chicks and its functional relationship to free amino acid metabolism in the brain. To understand the mechanism underlying the central function of brain amino acids in the feeding behavior of neonatal chicks, the interactions between appetite-related neuropeptides, amino acids, and their metabolites are discussed.

Precise feeding behavior of neonatal chicks and the putative role of amino acids as innate signals

Early studies described the frequent feeding patterns and brief bouts of feeding of domesticated chicks[11,12]. At the neonatal stage, the eating interval is very short compared to the adult stage, regardless of whether mammals or birds are altricial or precocial. The feeding behaviors of neonatal layer chicks are characterized by short resting periods with a very brief time spent on food intake[13]. A similar behavior was reported also in neonatal broiler chicks (Katayama et al., unpublished data). In contrast, time spent sleeping is longer in neonatal animals than in mature animals. Tran et al.[13] reported that the average time spent on food intake, sleeping, and resting by neonatal chicks was 10.9%, 17.5%, and 71.5%, respectively, over 6 h of observation. During the neonatal stage, animals spend time sleeping after ingesting food; thus, factors that inhibit food intake may induce sleep instead. In chickens, sleep can be assessed based on posture, such as sitting or standing motionless with eyes closed or with the head tucked under a wing[14]. Previous studies have demonstrated the central sedative and hypnotic functions of amino acids and their metabolites in neonatal chicks[10]. The effects of amino acids on sleep may be related to the control of feeding behavior, because feeding and sleep occur repeatedly. When neonatal chicks are centrally injected with L-pipecolic acid (L-PA), the reduction in active wakefulness, particularly feeding behavior, is accompanied by an increase in sleeping posture and a motionless state[15].

The concentration of circulating amino acids during the neonatal period is strongly affected by catabolism. This points to the importance of dynamic nutrient levels during this period[16]. Bird growth is associated not only with protein deposition, but also with the availability of free amino acids[17]. Amino acids are selectively transported from the blood to the brain, where they act as neurotransmitters or undergo specific metabolic transformations. In this review, the possible involvement of amino acids as central regulators of feeding behavior in neonatal chicks is described. Mellinkoff et al.[18] proposed an aminostatic concept for controlling food intake, based on an existing reciprocal relationship between serum amino acid content and appetite. In addition, fasting alters the concentration of free amino acids in several sites of the neonatal brain[19]. A recent study highlighted a linear correlation between free amino acid concentration in the plasma and different brain sites[6]. Tran et al.[13] demonstrated the frequent feeding behavior of neonatal chicks and initially observed differences in concentrations of amino acids and monoamines in the brain of chicks, who either attempted to obtain food (hungry group) or turned it down (satiety group). This sparked extensive investigation of the relationship between appetite regulation induced by fasting, subsequent short-term refeeding, and central amino acid metabolism[20]. The chicks were divided into four treatment groups: (i) fasting for 3 h and (ii–iv) fasting for 3 h, followed by refeeding for 10, 20, or 30 min. Even though refeeding was limited to a maximum of 30 min, it induced a rapid increase in several amino acids within chick brains. These findings suggest that free amino acids in the brain may contribute to the regulation of feeding behavior in neonatal chicks.

Evidence suggests that the amino acid content in the brain reflects the composition of dietary amino acids[21]. The uptake and concentration of amino acids by the brain are influenced by the availability of amino acids in the plasma, integrity of the blood-brain barrier, and complex interactions among amino acids[22,23]. Body homeostasis requires an optimal balance between dietary and circulating amino acids[16]. The above observations showcase how chickens are sensitive to the dietary intake of amino acids and respond accordingly, which is important when formulating an optimal diet.

Role of L-arginine metabolism in regulating food intake of neonatal chicks

L-Arginine is vital for protein synthesis and beyond[24]. In birds, it is an essential amino acid because these animals lack carbamoyl phosphate synthetase, a urea cycle enzyme necessary for the synthesis of citrulline from ornithine in the liver and kidney[25]. Diverse metabolites can be produced from L-arginine, including L-ornithine, L-proline, L-glutamic acid, polyamines, nitric oxide, creatine, and agmatine[26]. Under social separation stress conditions in chicks, L-arginine was reported to attenuate spontaneous activity and the number of distress vocalizations[27]. ICV injection of L-arginine attenuated the stress response in a dose-dependent manner and induced sleep-like behavior. Suenaga et al.[28] found increased L-arginine and L-ornithine levels in the telencephalon and diencephalon of chicks following the central administration of L-arginine 10 min post-injection. In addition, the increase in L-ornithine was proportional to that of injected L-arginine, suggesting that the latter was metabolized by arginases in the brain. The same study also demonstrated that L-ornithine might induce sedative and hypnotic effects. Thus, L-arginine metabolism is important for normal brain function.

In terms of food intake regulation, L-arginine and L-ornithine increased in a time-dependent manner in all parts of the brain following refeeding after fasting except for mesencephalic L-arginine and cerebellar L-ornithine[20]. Their central exogenous administration resulted in a dose-dependent feeding inhibitory effect only in chicks injected with L-ornithine[20]. This implies

that endogenous L-ornithine may act as a satiety signal in neonatal chicks.

To clarify the mechanism by which L-ornithine inhibited food intake in neonatal chicks, we investigated the involvement of γ-aminobutyric acid (GABA)-A receptor. Central injection of L-ornithine exerted sedative and hypnotic effects, mediated by the GABA-A receptor in neonatal chicks under stressful conditions[29]. However, the L-ornithine-induced reduction in food intake was not reversed by picrotoxin, a GABA-A receptor antagonist (Tran et al., unpublished data). Therefore, the mechanism by which L-ornithine controls feeding behavior is due to the non-responsiveness of stress-related pathways. At the same time, L-ornithine-induced sedation and hypnosis could occur along with the suppression of food intake. Evidence suggests that increased food intake inhibits sleep. For instance, ICV injection of kyotorphin, a central dipeptide, has been reported to stimulate food intake in chicks, together with increased peak efficiency and decreased time spent at deep rest[30]. Taken together, these results suggest that L-ornithine may suppress food intake due to its physiological effect on neurocircuits that control feeding behavior, while also causing sedation, in a GABA-A receptor-independent manner[20].

L-Proline is also increased in the telencephalon of neonatal chicks following ICV injection of L-arginine[28]. When ICV injected, L-proline spreads quickly within the brain of chicks[7], significantly decreasing their spontaneous activity and distress vocalization, while promoting a sleeping posture in a dose-dependent manner[19]. Although L-proline can activate the glycine receptor, it is not involved in consequent sedative or hypnotic effects[31]. Instead, the central functions of L-proline in neonatal chicks have been reported to involve several regulators, including the N-methyl-D-aspartic acid receptor[31] and indolamine metabolism[32]. In terms of food intake regulation, the concentration of L-proline in all brain parts of neonatal chicks increases in a time-dependent manner following refeeding after fasting[20]. Fasting for 3 h lowers the content of L-proline in the telencephalon and diencephalon of neonatal chicks[19]. Notably, ICV injection of L-proline stimulated food intake under ad libitum conditions, while inhibiting food intake under fasting conditions[33]. Hence, the mechanism by which L-proline regulates food intake in neonatal chicks remains unclear.

Feeding and other behaviors are associated with a sophisticated modulation of brain signals in neonatal chicks. For instance, central injection of carnosine not only inhibits food intake in a dose-dependent manner, but it also induces hyperactivity and increases plasma corticosterone levels[34]. However, the co-injection of β-alanine and L-histidine, the constituents of carnosine, also inhibited food intake but induced hypoactivity[34]. Therefore, it is important to understand the central function of L-arginine metabolism within the overall neural network controlling neonatal chick behavior. Central injection of L- and D-amino acids affects the behavior of neonatal chicks; although with varying effects and mechanisms[10]. The diverse impact of L-arginine and its enantiomer D-arginine was observed during isolation stress[35]. Specifically, ICV injection of L-arginine attenuated stress through induction of sedative and hypnotic effects; whereas ICV injection of D-arginine had a stimulatory effect. It is possible that L-arginine inhibits feeding behavior under stress, but not under normal physiological conditions, whereby L-ornithine achieves the same result. Adaptation to stress involves both behavioral and physiological changes in the central nervous system (CNS)[36]. The suppression of feeding behavior is a behavioral change induced by stress[37]. Because D-arginine is undetectable in the neonatal chick brains[35], the central effects of L-arginine may not be associated with physiological feeding behavior, but with the stress response, in a manner that is entirely independent of D-arginine.

The central role of other amino acids on food intake regulation

The end product of L-lysine metabolism, amino adipic acid, was also found to increase in all brain parts shortly after refeeding[20]. Activation of the L-lysine metabolic pathway following refeeding is thought to occur via L-PA, a major metabolic intermediate of L-lysine in the chick brain[38]. Akin to L-proline, L-PA altered food intake depending on feeding conditions. Central injection of L-PA significantly reduced the food intake of neonatal chicks under fasting conditions, although a higher dose of L-lysine was required to suppress food intake[15]. Instead, under ad libitum feeding conditions, ICV-injected L-PA stimulated feeding behavior[39]. GABA receptors contribute to the regulation of food intake by L-PA. In particular, the decrease in food intake caused by L-PA under fasting conditions is mediated by GABA-B receptors[40]; whereas stimulation of food intake by L-PA under ad libitum conditions is associated with both GABA-A and GABA-B receptors[39]. The enantiomer of L-PA, D-PA, has also been found to strongly decrease food intake in chicks, including at lower doses than L-PA[15].

L-Tryptophan is an essential amino acid, which functions as a precursor for several compounds via the serotonin (5-hydroxytryptamine, 5-HT) and kynurenine[10] pathways. Melatonin and 5-HT are products of the 5-HT pathway; whereas kynurenic acid (KYNA) is generated from l-kynurenine. Bungo et al.[41] reported that central injection of L-tryptophan reduced the food intake of neonatal layer chicks over 30 min of feeding, through a mechanism that involved the serotonergic system. Central 5-HT administration induces anorexia in chicks[42–44]. More than 95% of L-tryptophan is metabolized via the KYNA pathway[45]. KYNA appeared to have a stronger sedative effect than L-tryptophan under social isolation stress[46]. However, the effect of KYNA on the regulation of feeding behavior in neonatal chicks has not yet been clarified.

The feeding behavior of neonatal chicks is related also to other amino acids. Central injection of L-leucine significantly stimulated food intake; whereas L-isoleucine and L-valine had no effect[47]. Moreover, sedative and hypnotic responses have been reported in association with L-serine, L-glutamic acid, L-aspartic acid, and L-asparagine; although their effects on food

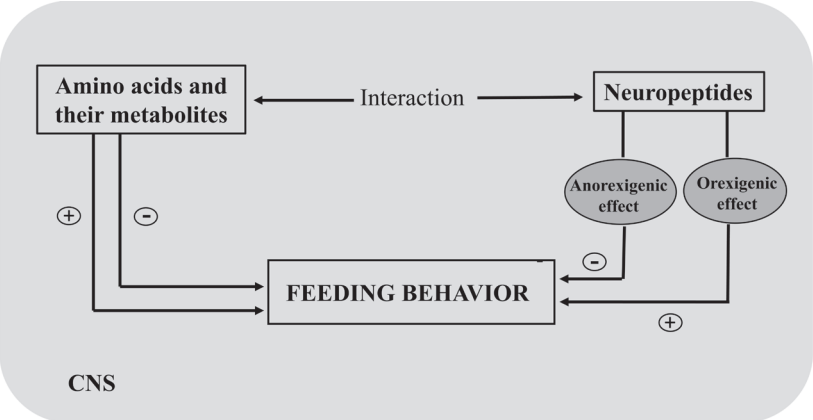

Fig. 1. **Schematic illustration of the central regulation of feeding behavior through neuropeptides and amino acids in neonatal chicks.** CNS, central nervous system; (+), stimulation; (-), inhibition.

intake regulation have not been confirmed.

Interactions between appetite-related neuropeptides and amino acids or their metabolites: the role of neuropeptide Y

Feeding behavior is tightly regulated by a series of neuronal, metabolic, and endocrine signals in the CNS[1,48]. The roles of numerous neuropeptides with orexigenic and anorexigenic effects in neonatal chicks have been already reviewed elsewhere[6]. The function and mechanism of neuropeptides has been compared between neonatal chicks and mammals, and between different strains of chickens. Although most neuropeptides induce similar feeding mechanisms in chicks and mammals, some have no or opposite effects[6]. Because the growth curve at the neonatal stage in animals is very steep, orexigenic signals were thought to be stimulated at this stage. Instead, more anorexigenic than orexigenic neuropeptides were detected in neonatal chicks[6]. However, because intense genetic selection has led to the production of broiler and layer chicks, food intake regulation differs between these two types, with the former displaying hyperphagia. The mechanism underlying this phenomenon can be explained by the involvement of neuropeptide activities, namely the lower synthesis of anorexigenic neuropeptides and modification of the receptor structure[6].

The contribution of neuropeptides to the regulation of food intake may be important in adult chickens, because the feeding interval is long enough for the actions of these compounds. At the neonatal stage, the feeding behavior is characterized by very short intervals of eating time, which is difficult to explain by the action of neuropeptides alone. Appetite regulation encompasses complex interactions between neurotransmitters, including neuropeptides and classical amino acid neurotransmitters, such as L-glutamic acid and GABA[49]. Accordingly, a possible collaboration between brain nutrient signals such as amino acids and appetite-related neuropeptides is hypothesized to regulate food intake in neonatal chicks (Fig. 1). Among orexigenic neuropeptides, neuropeptide Y (NPY) has been confirmed in both layers[50] and broiler chicks[51]. Since its first discovery in the CNS of chickens using antibodies against porcine NPY[52], growing evidence has pointed to the key regulatory role of NPY on feeding behavior in chickens[53–58]. Additionally, the NPY pathway is reportedly involved in the action of multiple feeding regulators[59]. Tran et al.[60] recently investigated interactions between NPY and L-ornithine in the neonatal chick brain and their role in controlling feeding behavior. In particular, the authors examined the role of L-ornithine signaling in the orexigenic effect induced by NPY. To this end, they evaluated food intake after direct central co-injection of NPY and L-ornithine. This, and an assessment of free amino acid metabolism in the central and peripheral systems of chicks, showed that L-ornithine induced significant dose-dependent suppression of NPY-elicited eating and correlated positively with brain L-ornithine levels.

The interaction between NPY and L-ornithine has been proposed to take several forms, all aimed at controlling food intake in neonatal chicks. Turton et al.[61] suggested that central NPY stimulated feeding by blocking inhibitory factors. Accordingly, L-ornithine may interact with NPY through several inhibitory signaling pathways originated from amino acid metabolism in the brain. This hypothesis is supported by changes in brain amino acid content following co-injection of NPY and L-ornithine. Notably, brain L-proline goes up when brain L-ornithine remains high following an increase in the injected dose. NPY may enhance the activity of ornithine aminotransferase and pyrroline-5-carboxylate reductase in the brain, because both enzymes contribute to the production of L-proline from L-ornithine. Second, a drop in L-methionine, a precursor of L-cysteine, and glycine was observed in chicks co-injected with NPY and L-ornithine. L-Ornithine is also converted to L-glutamic acid via ornithine

α-ketoglutarase aminotransferase. One possibility is that L-ornithine attenuates the orexigenic effect of NPY through the production of glutathione, a tripeptide consisting of L-glutamic acid, L-cysteine, and glycine, which was previously reported to inhibit food intake in neonatal chicks[62]. The third point to highlight is a decline in diencephalic L-tryptophan in chicks co-injected with NPY and L-ornithine. This finding implies a potent contribution of L-tryptophan catabolism to the interaction between NPY and L-ornithine in regulating feeding behavior in neonatal chicks. In contrast, in a study by Konishi et al.[63], the suppression of feeding by L-ornithine in rats involved the activation of hypothalamic pro-opiomelanocortin neurons, which stimulated the production of melanocortins. These act as anorexigenic factors in both mammals[64] and neonatal chicks[6]. Therefore, central NPY may interact either directly or indirectly with L-ornithine to mediate food intake in neonatal chicks.

Tran et al.[60] examined the effect of co-injecting NPY and L-ornithine on amino acid content in the peripheral system. Interestingly, the concentration of nearly all free amino acids in the plasma decreased significantly after a short but robust feeding period, stimulated by injection of NPY. A reduced free amino acid pool implies enhanced transfer of free amino acids to the body protein pool, suggesting that central NPY may stimulate protein synthesis in chicks. The concentration of free amino acids in the plasma was further reduced upon co-administration of NPY and L-ornithine. Hence, L-ornithine present in the CNS may be a regulator of protein metabolism. On the other hand, Tachibana et al.[65] reported that NPY shifted the utilization of metabolic fuels from carbohydrates to lipids and proteins. Nevertheless, further studies are required to determine the effects of NPY and L-ornithine on protein metabolism.

Tran et al.[13] associated altered brain monoamine levels with frequent feeding behavior in neonatal chicks. Catecholamines have been shown to be unequivocally involved in the regulation of food intake in avian species, as evidenced by their elevated content in the brains of birds[66]. NPY co-localizes with catecholaminergic neurons that project to the paraventricular nucleus of the hypothalamus[67]. In chickens, co-injection of NPY and clonidine, an α_2-adrenoceptor agonist, resulted in the attenuation of NPY-induced feeding[68]. Instead, co-injection of NPY with yohimbine, an adrenergic α_2-receptor antagonist, diminished the orexigenic effect of NPY[69]. Tran et al.[70] investigated the interaction between NPY and brain monoamine metabolism in the regulation of feeding behavior under either ad libitum feeding or fasting conditions. The results showed that central injection of NPY significantly increased dopamine metabolites, including 3,4-dihydroxyphenylacetic acid and homovanillic acid, while significantly attenuating diencephalic gene expression of catecholaminergic synthetic enzymes, such as tyrosine hydroxylase, L-aromatic amino acid decarboxylase, and GTP cyclohydrolase I, under ad libitum feeding conditions, but not under fasting conditions. In contrast, central NPY did not influence indolamine metabolism in chicks. Thus, it is possible that NPY exerts an orexigenic effect by activating dopaminergic neurons and downstream dopamine metabolism, while modulation of NPY in the catecholaminergic system is mediated by nutrients through food intake.

Conclusions and future perspectives

The regulation of feeding behavior in neonatal chicks involves multiple interactions and a synergistic action between endogenous neuropeptides, endogenous and/or exogenous nutrients such as amino acids and their metabolites.

The central function of L-arginine metabolism is manifested by the role of its metabolite, L-ornithine, in regulating feeding behavior in the chick brain. The specific receptor mediating the inhibitory effect of L-ornithine on feeding in the CNS should be further investigated to better understand the relationship between endogenous L-ornithine and other brain amino acids involved in the physiological regulation of food intake.

Neural circuits involved in the regulation of feeding behavior have been extensively reviewed[4,6], and there is evidence for the contribution of non-neural cells, such as glial cells, to neuronal circuits associated with appetite[71,72]. Neuroglia can modulate synaptic neurotransmission by releasing several amino acids as gliotransmitters[73]. Therefore, it is important to explore these histochemical aspects in future studies on the control of feeding behavior.

Adequate provision of dietary amino acids is essential for optimal efficiency in poultry production[74]. The early stage of growth is crucial for animal health and performance. The key role played by amino acids in the overall network of the neonatal chick CNS can be used to adjust dietary amino acids for optimal performance in poultry production and to attain further insights on appetite biology across species.

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Conflicts of interest

The author declares no conflict of interest.

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