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To cite this article: M. Zendehdel, F. Sardari, S. Hassanpour, M. Rahnema, A. Adeli & E. Ghashghayi (2017) Serotonin-induced hypophagia is mediated via $\alpha_2$ and $\beta_2$ adrenergic receptors in neonatal layer-type chickens, British Poultry Science, 58:3, 298-304, DOI: 10.1080/00071668.2017.1278626

To link to this article: http://dx.doi.org/10.1080/00071668.2017.1278626

Published online: 31 Mar 2017.
Serotonin-induced hypophagia is mediated via $\alpha_2$ and $\beta_2$ adrenergic receptors in neonatal layer-type chickens

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ABSTRACT
1. Serotonergic and adrenergic systems play crucial roles in feed intake regulation in avians but there is no report on possible interactions among them. So, in this study, 5 experiments were designed to evaluate the interaction of central serotonergic and adrenergic systems on food intake regulation in 3 h food deprived (FD) 3 neonatal layer-type chickens. 2. In Experiment 1, chickens received intracerebroventricular (ICV) injection of control solution, serotonin (56.74 nmol), prazosin ($\alpha_2$ receptor antagonist, 10 nmol) and co-injection of serotonin plus prazosin. In Experiment 2, control solution, serotonin (56.74 nmol), yohimbine ($\alpha_2$ receptor antagonist, 13 nmol) and co-injection of serotonin plus yohimbine were used. In Experiment 3, the birds received control solution, serotonin (56.74 nmol), metoprolol ($\beta_1$ receptor antagonist, 24 nmol) and co-injection of serotonin plus metoprol. In Experiment 4, injections were control solution, serotonin (56.74 nmol), ICI 118.551 ($\beta_2$ receptor antagonist, 5 nmol) and serotonin plus ICI 118.551. In Experiment 5, control solution, serotonin (56.74 nmol), SR59230R ($\beta_2$ receptor antagonist, 20 nmol) and co-administration of serotonin and SR59230R were injected. In all experiments the cumulative food intake was measured until 120 min post injection. 3. The results showed that ICV injection of serotonin alone decreased food intake in chickens. A combined injection of serotonin plus ICI 118.551 significantly attenuated serotonin-induced hypophagia. Also, co-administration of serotonin and yohimbine significantly amplified the hypophagic effect of serotonin. However, prazosin, metoprol and SR59230R had no effect on serotonin-induced hypophagia in chickens. 4. These results suggest that serotonin-induced feeding behaviour is probably mediated via $\alpha_2$ and $\beta_2$ adrenergic receptors in neonatal layer-type chicken.

Introduction
Nowadays, several neurotransmitters involved in appetite regulation have been identified; among them are serotonergic (5-HTergic) and adrenergic systems (Hassanpour et al., 2015). One of the main neurotransmitters known to be involved in feeding behaviour in avian species is serotonin (5-hydroxytryptamine (5-HT); El-Merahbi et al., 2015). Serotonin is a bioamine which produces from the amino acid tryptophan in the brain, it serves as a neurotransmitter and regulates multiple physiological aspects including behaviour, learning and appetite (Mortezaei et al., 2013; El-Merahbi et al., 2015).

The 5-HT has catabolic effects on energy homeostasis, reducing food intake and stimulating energy expenditure in mammals (Telles et al., 2013). Investigations showed that intracerebroventricular (ICV) injection of 5-HT induces a decrease in food intake in avians (Denbow et al., 1982; Denbow, 1984, 1989; Mortezaei et al., 2013; Zendehdel et al., 2013). Adrenergic receptors belong to the G protein-coupled receptor subtypes (GPCRs). To date 5 subtypes of adrenergic receptors have been identified. The two known $\alpha$ adrenergic receptors are $\alpha_1$ and $\alpha_2$ and the three known $\beta$ adrenergic receptor subtypes are designated $\beta_1$, $\beta_2$ and $\beta_3$ (Hoffmann et al., 2004). Activation of $\alpha_2$ adrenergic receptors by noradrenaline induces eating and this has been linked to disinhibition of descending “satiety” fibres that project caudally from the paraventricular nucleus (PVN) (Wellman, 2000).

The inhibitory effects of noradrenaline on PVN cells were mimicked by administration of the $\alpha_2$ adrenergic receptor agonist, clonidine, while the inhibitory effects of noradrenaline were reversed using a $\alpha_2$ adrenergic receptor antagonist, yohimbine (Wellman, 2000). So, these results suggest $\alpha_2$ receptors might have an orexigenic effect on feeding behaviour (Wellman, 2000). Noradrenaline could also modulate food intake via $\beta_1$ or $\beta_2$ adrenergic receptors where ICV injection of salbutamol, a $\beta_2$ adrenergic receptor agonist, decreased food consumption while ICV administration of $\beta_2$ adrenergic receptor antagonists increased food intake in rats (Kanzler et al., 2011). Distribution of adrenergic receptors varies in the different parts of the domestic fowl brain. The $\alpha_2$ adrenergic receptors increase food intake, whereas $\beta_2$ and $\beta_3$ adrenergic receptors decrease food and water intake in poultry (Baghbanzadeh and Hajinezhad, 2010).

Elaborate physiological mechanisms control food intake, including the interplay between neuropeptidergic pathways (Olszewski and Levine, 2004; Zendehdel et al., 2013). Neural axons in raphe nuclei form a neurotransmitter system reaching several parts of the brain. Axons of neurons in the lower raphe nuclei are terminated in the spinal cord and...
Beta-adrenergic systems might be playing a role in the adrenergic systems on appetite regulation in neonatal layer-type birds (each experiment included 4 groups within 12 replicates in each group; $n = 48$). Prior to each experiment, the chickens were weighed and based on their body weight divided into experimental groups so the average weight between treatment groups was as uniform as possible. The ICV injections were done using a microsyringe (Hamilton, Biel/Bienne, Switzerland) without anaesthesia in accordance to the technique described by Davis et al. (1979) and Furuse et al. (1997) in which the head of the bird was held with an acrylic device while the bill holder was 45° and calvarium parallel to the surface of the table (Van Tienhoven and Juhasz, 1962). A plate with a hole was laid over the right lateral ventricle and a hole was drilled through the skull. A microsyringe was inserted into the right ventricle through the hole and tip of the needle penetrated 4 mm beneath the skin of the skull. There is no injection-induced physiological stress by this technique in neonatal chickens (Saito et al., 2005). All injections were done in a volume of 10 μl (Furuse et al., 1999). The control group received control solution (saline containing Evans blue 10 μl) (Furuse et al., 1999). Right after injection, FD3 fowls were returned to their individual cages and supplied with fresh water and food (pre-weighed). In this study, a uniform timetable was used to food deprive and subsequently inject the subjects. Briefly, the birds were food deprived with a 3-min gap to each other. Then after 3 h, the same schedule was used for injection with the first bird injected after 3 h and the next one 3 min later and so on. Then cumulative food intake (g) was measured individually at 30, 60 and 120 min post injection. In this manner, the effect of fluctuation in time during FD3, injection and time for food consumption is avoided. Food consumption (plus any food spillage) was calculated as a percentage of body weight to minimise impact of body weight on the amount of food intake. Each bird was used just once in each experimental group. Chicken were killed by decapitation after the experiment. Accuracy of placement of the injection in the ventricle was verified by the presence of Evans blue followed by slicing the frozen brain tissue. In each group, 12 birds received injection, but just data of individuals where dye was present in their lateral ventricle were used for analysis (9–12 chickens per group). When the first experiment was finished, the next experiment started. All experimental procedures were done from 8:00 A.M. until 3:30 P.M. The time course of food consumption was estimated based on previous studies (Alizadeh et al., 2015; Jonaidi and Noori, 2012; Zendehdel and Hassanpour, 2014; Alimohammadi et al., 2015; Hassanpour et al., 2015).

### Materials and methods

#### Animals

A total of 240-d-old female layer-type chickens (Hy-Line) were purchased from a local hatchery (Morghak Co., Tehran, Iran). The chickens were kept in a flock for 2 d and then randomly transferred into individual cages and kept at a temperature of 30 ± 1°C with 50 ± 2% humidity (Olanrewaju et al., 2006). Animal handling and experimental procedures were performed according to the Guide for the Care and Use of Laboratory Animals by the National Institute of Health (U.S.A.) and the current laws of the Iranian Government for animal care. A commercial diet provided during the study containing 21% crude protein and 11.9 MJ/kg of metabolisable energy (Chineh Co., Tehran, Iran). All chickens were offered ad libitum food and fresh water during the study. Just 3 h prior the ICV injections, chickens were food deprived (FD3) but had free access to fresh water. The injections were applied to all birds at 5 d of age.

#### Experimental drugs

Serotonin (Serotonergic agonist), prazosin (α1 receptor antagonist), yohimbine (α2 receptor antagonist), metoprolol (β1 receptor antagonist), ICI 118.551 (β2 receptor antagonist), SR59230R (β3 receptor antagonist) and Evans blue were all produced by Sigma-Aldrich (St. Louis, U.S.A.). Drugs were at first dissolved in absolute dimethyl sulphoxide (DMSO) and then diluted with 0.85% control solution (saline) containing Evans blue at a ratio of 1/250 control solution.

#### ICV injection procedures

In this study, 5 experiments were performed to determine possible interconnection(s) of central 5-HTergic and adrenergic systems on appetite regulation in neonatal layer-type chickens, whereas axons of the higher nuclei spread out in the entire brain, such as the arcuate nucleus (ARC) (Frazier and Hensler, 1999).

Noradrenalin excites approximately half of the neurons in the ARC, probably because of a direct postsynaptic response via α or β receptors (Date et al., 2006). It is suggested, that central effects of NPY and α2 adrenergic systems might be altered depending on their concentrations in the young chick. Neuropeptide Y can increase α2 adrenergic binding sites in the CNS (Furuse, 2002). 5-HT directly activates POMC cleavage and inhibits NPY and AgRP at the ARC (Feijó et al., 2011).

Central food intake regulatory factors in the brain are somewhat different between mammals and birds. For example, ghrelin is known as an orexigenic factor in mammals while it is an anorexigenic peptide in chicken (Zendehdel and Hassanpour, 2014). Scarce information is available on the central interplay of these systems on food intake regulation. Evidences indicate an antagonistic interaction between hypothalamic 5-HT and α2 adrenergic receptor systems (Weiss et al., 1986). We hypothesised that the hypophagic effect of the 5-HTergic system possibly modulates via α1, α2, β1, β2 and β3 adrenergic receptors in 3 h food-deprived neonatal layer-type chicken.

#### Food intake measurement procedure

A total of 5 experiments were designed, each with 4 treatment groups: A, B, C and D, groups ($n = 48$ in each experiment, Table). In Experiment 1, chickens received ICV injection of (A) control solution, (B) serotonin (serotonergic agonist, 56.74 nmol), (C) prazosin (α1 receptor antagonist, 10 nmol) or (D) co-injection of serotonin + prazosin. In Experiment 2, birds were ICV injected with (A) control solution, (B) serotonin (56.74 nmol), (C) yohimbine (α2 receptor antagonist, 13 nmol) or (D) serotonin + yohimbine. In Experiment 3, birds received ICV injections of (A) control solution, (B) serotonin (56.74 nmol), (C) metoprolol (β1 receptor antagonist,
24 nmol) or (D) co-injection of serotonin + metoprolol. In Experiment 4, injections were (A) control solution, (B) serotonin (56.74 nmol), (C) ICI 118.551 (5 nmol) or (D) serotonin + ICI 118.551. In Experiment 5, birds were ICV injected using (A) control solution, (B) serotonin (56.74 nmol), (C) SR59230R (20 nmol) or (D) co-administration of serotonin + SR59230R. To examine the possible interactions between these two systems, effective and sub-effective doses of pharmacologic agents were administered to confront nullifying effects of the agents. In other words, when an effective dose of a system is administered, on the other hand the sub-effective dose of the other system must be considered. These doses of drugs were determined according to previous studies (Baghbanzadeh and Hajinezhad, 2010; Zendehdel et al., 2012, 2013; Mortezaei et al., 2013; Zendehdel and Hassanpour, 2014) and own pilot studies (unpublished).

**Statistical analysis**

Cumulative food intake (% of BW) was analysed by factorial analysis of variance (ANOVA) using SAS 9.1 for Windows and is presented as mean ± SEM. For treatments showing a main effect by ANOVA, means were compared using *post hoc* Duncan’s Multiple Range Test. *P* < 0.05 was considered as significant differences between treatments.

**Results**

Effects of interaction between 5-HTergic and noradrenergic systems on cumulative food intake in FD3 neonatal layer-type chickens are shown in Figures 1–5.

In Experiment 1, ICV injection of an effective dose of a 5-HTergic agonist (serotonin, 56.74 nmol) significantly decreased food intake (% BW) in comparison to the control group (*F*(1,42) = 73.09, *P* < 0.001). The ICV injection of a

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**Table** Treatments procedures in the experiments.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Treatment groups</th>
<th>ICV injection</th>
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<tbody>
<tr>
<td>1</td>
<td>A CS*</td>
<td></td>
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<tr>
<td></td>
<td>B Serotonin (56.74 nmol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C Prazosin (10 nmol)</td>
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<td></td>
<td>D Serotonin (56.74 nmol) + prazosin (10 nmol)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>A CS*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B Serotonin (56.74 nmol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C Yohimbine (13 nmol)</td>
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</tr>
<tr>
<td></td>
<td>D Serotonin (56.74 nmol) + yohimbine (13 nmol)</td>
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</tr>
<tr>
<td>3</td>
<td>A CS*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B Serotonin (56.74 nmol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C Metoprolol (24 nmol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D Serotonin (56.74 nmol) + metoprolol (24 nmol)</td>
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<tr>
<td>4</td>
<td>A CS*</td>
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<tr>
<td></td>
<td>B Serotonin (56.74 nmol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C ICI 118.551 (5 nmol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D Serotonin (56.74 nmol) + ICI 118.551 (5 nmol)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>A CS*</td>
<td></td>
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<tr>
<td></td>
<td>B Serotonin (56.74 nmol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C SR59230R (20 nmol)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D Serotonin (56.74 nmol) + SR59230R (20 nmol)</td>
<td></td>
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</tbody>
</table>

CS*: control solution; Serotonin: Serotonergic agonist; Prazosin: α1 receptor antagonist; Yohimbine: α2 receptor antagonist; Metoprolol: β1 receptor antagonist; ICI 118.551: β2 receptor antagonist; SR59230R: β3 receptor antagonist.

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Figure 1. Effect of ICV injection of serotonin (56.74 nmol), prazosin (10 nmol) and their combination on per cent of body weight cumulative food intake in neonatal layer-type chickens. Serotonin: Serotonergic agonist; prazosin: α1 receptor antagonist. There are significant differences between groups with different superscripts in a column (a and b; *P* < 0.001).

Figure 2. Effect of ICV injection of serotonin (56.74 nmol), yohimbine (13 nmol) and their combination on per cent of body weight cumulative food intake in neonatal layer-type chickens. Serotonin: Serotonergic agonist; yohimbine: α2 receptor antagonist. There are significant differences between groups with different superscripts in a column (a, b and c; *P* < 0.001).

Figure 3. Effect of ICV injection of serotonin (56.74 nmol), metoprolol (24 nmol) and their combination on per cent of body weight cumulative food intake in neonatal layer-type chickens. Serotonin: Serotonergic agonist; metoprolol: β1 receptor antagonist. There are significant differences between groups with different superscripts in a column (a and b; *P* < 0.001).

Figure 4. Effect of ICV injection of serotonin (56.74 nmol), ICI 118.551 (5 nmol) and their combination on per cent of body weight cumulative food intake in neonatal layer-type chickens. Serotonin: Serotonergic agonist; ICI 118.551: β2 receptor antagonist. There are significant differences between groups with different superscripts in a column (a, b and c; *P* < 0.001).
sub-effective dose of the α₁ receptor antagonist (prazosin, 10 nmol) had no effect on food intake compared with the control group (F(l,42) = 0.59, P > 0.05). Co-injection of 5-HT plus prazosin had no effect on 5-HT-induced hypophagia in neonatal layer-type chickens (Time, F(2,73) = 68.35, P < 0.001; prazosin and serotonin interaction, F(l,42) = 1.38, P > 0.05) (Figure 1).

In Experiment 2, ICV injection of a sub-effective dose of the α₂ receptor antagonist (yohimbine, 13 nmol) had no effect on cumulative food intake compared with the control group (F(l,39) = 1.86, P > 0.05). Co-administration of 5-HT plus yohimbine significantly amplified the significant hypophagic effect of 5-HT (Time, F(2,85) = 113.01, P < 0.001; yohimbine and serotonin interaction, F(l,39) = 89.27, P < 0.001) (Figure 2).

In Experiment 3, ICV administration of an effective dose of 5-HT (56.74 nmol) significantly decreased food intake in comparison with the control group (F(l,56) = 64.92, P < 0.001). A sub-effective dose of metoprolol was not able to alter 5-HT-induced hypophagia in chickens (F(l,56) = 2.58, P > 0.05). Also, co-injection of 5-HT plus metoprolol was not able to alter 5-HT-induced hypophagia in chickens (Time, F(2,81) = 93.07, P < 0.001; metoprolol and serotonin interaction, F(l,56) = 0.81, P > 0.05) (Figure 3).

In Experiment 4, ICV injection of sub-effective dose of β₂ receptor antagonist (ICI 118.551, 5 nmol) had no effect on food intake compared with the control group (F(l,29) = 1.36, P > 0.05). ICV administration of 5-HT (56.74 nmol) significantly diminished food intake in chickens (F(l,29) = 114.35, P < 0.001). Interestingly, co-injection of ICI 118.551 plus 5-HT significantly minimised the hypophagic effect of 5-HT in neonatal layer-type chickens (Time, F(2,64) = 78.14, P < 0.001; ICI 118.551 and serotonin interaction, F(l,29) = 136.15, P < 0.001) (Figure 4).

According to the results of Experiment 5, ICV administration of 5-HT (56.74 nmol) significantly decreased food consumption in neonatal layer-type chickens (F(l,46) = 94.17, P < 0.001). ICV injection of the β² receptor antagonist (SR59230R, 20 nmol) had no effect on food intake compared with the control group (F(l,46) = 0.74, P > 0.05). Also, co-injection of 5-HT plus SR59230R had no effect on 5-HT-induced hypophagia in neonatal chickens (Time, F(2,75) = 82.45, P < 0.001; SR59230R and serotonin interaction, F(l,46) = 2.34, P > 0.05) (Figure 5).

Discussion

To the best of our knowledge, this is the first report on interactions between 5-HTergic and adrenergic systems in reward regulation in FD3 neonatal layer-type chickens (Figure 6). According to the results obtained from Experiments 1–5, 5-HT decreased food intake in FD3 chickens, which was in agreement with prior studies on ICV injection of 5-HT, and caused a significant decrease in food intake (Zendehdel et al., 2012, 2013; Mortezaei et al., 2013). 5-HT receptors have existed in animal cells for millions of years and they are as old as adreno-receptors. Even in invertebrates, such as molluscs (Aplysia californica), annelids (Hirudo medicinalis) and in the honey bee, 5-HT might functionally be related to food intake (Voigt and Fink, 2015). Studies demonstrated that 5-HT acts on various receptor subtypes and the hypophagic effects of ICV injection of 5-HT is mediated through 5-HT₂a and 5-HT₂c receptors (Saadoun and Cabrera, 2002). So, based on previous studies on the role of 5-HT receptor subtypes on food intake in birds, in this study, ICV injection of 5-HT was used as an anorexigenic neurotransmitter to investigate its possible interconnection with adrenergic receptor subtypes (α₁, α₂, β₁, β₂ and β₃) on feeding behaviour in neonatal layer-type chicken.

As observed, ICV injection of sub-effective doses of α₁ and α₂ receptors antagonists had no effect on food intake. ICV injection of noradrenaline inhibits ingestion in chicken (Bungo et al., 2001). On the other hand, ICV injection of clonidine, an α₂ adrenergic receptor agonist, resulted in stimulation of feeding in chickens (Bungo et al., 1999). The α₂ adrenergic receptor agonist decreases noradrenergic signalling by stimulating inhibitory pre-synaptic α₂ adrenergic receptors and this decreased feeding and drinking behaviour in rats. Noradrenaline excites approximately half of the neurons in the ARC, probably because of a direct postsynaptic response via α or β receptors (Rasmussen et al., 2014). In contrast, it is reported that ICV injection of α₂ receptor agonists abolished sodium and water intake and this effect was still present after the injection of a 5-HTergic antagonist (Margatho et al., 2002). The noradrenergic inputs to the raphe nucleus exert tonic facilitator control

![Figure 5](image56x673). Effect of ICV injection of serotonin (56.74 nmol), SR59230R (20 nmol) and their combination per cent of body weight cumulative food intake in neonatal layer-type chickens. Serotonin: Serotonergic agonist, SR59230R: β₂ receptor antagonist, 20 nmol. There are significant differences between groups with different superscripts in a column (a and b; P < 0.001).

![Figure 6](image56x809). Interaction between adrenergic and 5-HTergic systems on central appetite regulation centres in the poultry brain. As seen the projections of the 5-HTergic and noradrenergic systems not only reach to the feeding sites in the arcuate nucleus (ARC), but also interplay with each other to regulate food intake (Richards and Proszkowiec-Wegljarz, 2007). POMC: proopiomelanocortin; NPY: neuropeptide Y; AgRP: agouti-related peptide.
of 5-HT release via $\alpha_1$ and $\alpha_2$ adrenergic receptors (Ribas et al., 2012). ICV injection of clonidine (an $\alpha_2$ adrenergic agonist) into the median raphe nucleus of free-feeding rats resulted in a hyperphagic response (Mansur et al., 2010). So, a possible neural interconnection might exist between 5-HTergic and adrenergic systems via $\alpha_2$ receptors. Blier et al. (1990) reported, there was interconnection between $\alpha_2$ adrenergic heteroreceptors and 5-HT uptake inhibitors in the rat hypothalamus. $\alpha_2$ adrenergic receptors tonically inhibit the 5-HT release, and blockade of $\alpha_2$ adrenergic receptors strikingly potentiate the increased levels of 5-HT by reuptake inhibitors in the frontal cortex of rats (Gilsbach et al., 2009). Thus, the blockade of $\alpha_2$ adrenergic receptors may reinforce the efficacy of monoamine uptake inhibitors (Gobert et al., 1997). ICV injection of $\alpha_2$ adrenergic receptors antagonist might reinforce the hypophagic effect of the 5-HTergic system by a blocking effect on $\alpha_2$ adrenergic receptors in birds. Further investigation is needed to clarify the direct mechanism of action among these two neural pathways.

Herein, co-injection of 5-HT and ICI 118.551 (a $\beta_2$ receptor antagonist) significantly diminished the hypophagic effect of 5-HT but no interaction was detected between 5-HT and $\beta_1$ and $\beta_3$ receptors. Effects of $\beta$ adrenergic receptors on body metabolism and appetite have been detected previously. Stimulation of avian $\alpha_2$ adrenergic receptors increased food intake whereas stimulation of $\beta$ adrenergic receptors reduce food and water intake (Baghbanzadeh and Hajinezhad, 2010). Food intake increased via $\alpha_1$ and $\alpha_2$ adrenergic agonists in broilers and layers while $\beta_2$ agonists reduced food intake of chickens under ad libitum (not fasting) feeding conditions (Baghbanzadeh et al., 2015). It seems the effect of noradrenaline on feeding is depending on the receptor subtype (Tachibana et al., 2003).

Non-selective $\beta$ adrenocceptor antagonists decrease 5-HT-mediated responses, maybe by direct blockade of 5-HT receptors. This finding promotes the possibility that $\beta$ adrenocceptor agonists may produce their enhancement of 5-HT-mediated responses by interacting directly through the 5-HT systems in the brain (Cowen et al., 1982). Noradrenalin excites approximately half of the neurons in the ARC, probably because of a direct postsynaptic response via $\alpha$ or $\beta$ receptors (Valassi et al., 2008; Crespo et al., 2014). There is recent evidence that 5-HT receptors inhibit the activity of NPY/AgRP neurons in the ARC (Date et al., 2006; Heisler et al., 2007; Richards and Proszkwiec-Weglarz, 2007) (Figure 6). The 5-HT directly activates POMC cleavage. Furthermore, 5-HT$_2$B receptor inhibits the NPY and AgRP at the ARC, depressing GABAergic inhibiting transmission of $\alpha$-melanotropin and the CART (De Matos Feijó et al., 2011).

The dynamic interplay between 5-HT and the adrenergic system has been extensively studied over the past decades. However, the direct mechanism of this interaction has not been identified. It seems, there are further mechanisms underlying this interplay. Presumably, hypothalamic–pituitary–adrenal (HPA) axis interplay is dynamic between these systems (Heisler et al., 2007). For example, in $\beta_3$ adrenergic receptor knockout mice, injection of $\beta_3$ receptor agonists into white fat blocks the reduction in food intake, indicating peripheral $\beta_3$ adrenergic receptors are involved in the modulation of food intake (Bray, 2000). As observed in this study, $\beta_3$ receptors had no interconnection with 5-HT on food intake regulation in neonatal layer-type chicken. In the current study, birds were given just a 3-h fasting period before initiation of the study. Presumably, $\beta_3$ receptors act after a longer period of food deprivation and perhaps via the remnin-angiotensin system and adrenergic circuitry, especially in elucidating central mechanisms regulating water intake. However, the accuracy of this hypothesis will be the potential subjects for future studies (Baghbanzadeh and Hajinezhad, 2010).

To our knowledge, there was no previous study on the role of central 5-HTergic and adrenergic systems on food intake in avians, so it was not possible to compare the current results with previous studies. These present results suggest serotonin-induced feeding behaviour is probably mediated via $\alpha_2$ and $\beta_2$ adrenergic receptors in neonatal layer-type chickens. Most research on central food intake regulation has been done with rat models, whereas comparatively few investigations were done in birds. The present observations can be used as base information on central food intake regulation in birds. Finally, the authors recommend further investigations to clarify the direct cellular and molecular signalling pathways of 5-HTergic and adrenergic systems with other receptors and their role in the physiology of food intake regulation in poultry.

Acknowledgements

This research was supported by a grant from the Research Council of the Faculty of Veterinary Medicine, University of Tehran, Iran. This manuscript does not contain any studies with human subjects performed by any of the authors. All experiments were executed according to the Guide for the Care and Use of Laboratory Animals (NIH publication No. 85-23, revised 1996) and approved by the institutional animal ethics committee.

Disclosure statement

M. Zendehdel, F. Sardari, S. Hassanpour, M. Rahnema, A. Adeli and E. Ghashghayi declare that they have no conflict of interest.

Funding

This work was supported by the Research Council of the Faculty of Veterinary Medicine, University of Tehran.

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