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European Journal of Pharmacology 427 (2001) 53–59

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Feeding responses to several neuropeptide Y receptor agonists in the neonatal chick

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Received 19 March 2001; received in revised form 3 July 2001; accepted 10 July 2001

Abstract

Neuropeptide Y is one of the most potent neuropeptides known to induce feeding in animals, and has been suggested to be a physiological signal for food intake. It has been also reported that intracerebroventricular injection of neuropeptide Y stimulates feeding behavior of the neonatal chick. There are many neuropeptide Y receptor agonists that have not been investigated in feeding response of the neonatal chick. The aim of this study is to elucidate whether central injection of several neuropeptide Y receptor agonists stimulates feeding of the neonatal chick over 2 h. We found that central injections of [Leu^{31}, Pro^{34}]neuropeptide Y, peptide YY, human pancreatic polypeptide and rat pancreatic polypeptide significantly stimulated food intake of neonatal chicks throughout the 2-h post-injection period. Neuropeptide Y-(13–36) significantly stimulated feeding at 30 min, but not thereafter. [D-Trp^{32}]neuropeptide Y stimulated feeding at 60 and 120 min, but not 30 min, post-injection. Central administration of rat pancreatic polypeptide, which does not increase food intake in rats, stimulated feeding in chicks. This result reflects structural differences of the neuropeptide Y receptor subtypes and/or differences in mechanisms stimulating feeding behavior between mammals and chickens. In conclusion, neuropeptide Y receptor agonists, except for neuropeptide Y-(13–36), are potent stimulators of food intake in the neonatal chick.

Keywords: Neuropeptide Y; Intracerebroventricular injection; Food intake, chick

1. Introduction

Neuropeptide Y, orexin-A, orexin-B, motilin, melanin-concentrating hormone, galanin, growth hormone releasing factor and ghrelin are reported to stimulate food intake in rats (Clark et al., 1984; Sakurai et al., 1998; Rosenfeld and Garthwaite, 1986; Qu et al., 1996; Kyrkouli et al., 1986; Vaccarino, 1990; Tschop et al., 2000). In the chicken, neuropeptide Y stimulates food intake similar to mammals (Kuenzel et al., 1987; Kuenzel and McMurtry, 1988; Furuse et al., 1997). However, both orexins, motilin, melanin-concentrating hormone and galanin failed to alter food intake of the chick (Furuse et al., 1999; Ando et al., 2000). Moreover, growth hormone releasing factor and ghrelin suppressed feeding of chicks (Furuse et al., 2001). These facts suggest that orexigenic effects of neuropeptides, except for neuropeptide Y, are more recent developments in the course of the evolution first acting in mammalian species. The effect of neuropeptide Y on feeding is common over many species. Therefore, elucidating the mechanisms by which neuropeptide Y stimulates feeding in the chicken should provide important insight into the neurochemical control of feeding across species.

Neuropeptide Y is a highly conserved neuropeptide involved in the regulation of several neuroendocrine functions, including feeding and drinking, central autonomic functions, learning, stress responses, and sexual and motor behaviors (Gray and Morley, 1986). Neuropeptide Y is widely distributed within the peripheral and central nervous system (Tatemoto, 1982a,b; Gray and Morley, 1986). When neuropeptide Y is administered centrally, it stimulates food intake in rats and mice (Clark et al., 1984; Gray and Morley, 1986; Morley et al., 1987; Stanley et al.,

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0014-2999/01/$ - see front matter
PII: S0014-2999(01)01201-8

1992). In fact, neuropeptide Y is one of the most potent neuropeptides known to induce feeding in animals (Leibowitz and Alexander, 1991; Lynch et al., 1994; Nakajima et al., 1994) and has been suggested to be a physiological signal for food intake (Dube et al., 1994; Sahu et al., 1997). Chronic administration of neuropeptide Y into the lateral ventricle or direct injection into the paraventricular nucleus of the rat increases food intake and leads to obesity (Stanley et al., 1986; Vettor et al., 1994). The obese Zucker rat is known to possess a hyperactive hypothalamic neuropeptide Y system (McCarthy et al., 1991; Dryden et al., 1995; Widdowson, 1997), and the genetically obese *ob / ob* mouse expresses higher levels of neuropeptide Y mRNA in the hypothalamus (Wilding et al., 1993). Erickson et al. (1996) suggested a significant role for neuropeptide Y in hyperphagia and obesity.

Neuropeptide Y appears to exert its actions via multiple receptor subtypes. The neuropeptide Y receptors couple to G-proteins and include five cloned subtypes in mammalians, named neuropeptide Y Y_1–Y_6 receptor subtypes (neuropeptide Y Y_3 receptors not yet cloned). The neuropeptide Y family of peptides, which includes endogenous peptides, peptide YY and pancreatic polypeptide, as well as several N-terminal truncated and synthetic peptide agonists ([Leu^{31}, Pro^{34}]neuropeptide Y, neuropeptide Y-(13–36), [D-Trp^{32}]neuropeptide Y), have differential in vitro affinity to neuropeptide Y Y_1–Y_6 receptor subtypes (Corp, 1996; Blomqvist and Herzog, 1997). Neuropeptide Y has moderate to high affinity for all of the receptor subtypes. Endogenous neuropeptide Y occurs as neuropeptide Y-(1–36) in the brain (Stenfors et al., 1997). Various neuropeptide Y receptor agonists have been used to determine which receptor mediates the orexigenic action of neuropeptide Y in mammalian brain. Affinities of these agonists at mammalian five neuropeptide Y receptors were clarified in vitro. Moreover, it has been reported that activation of the neuropeptide Y Y_5 receptor regulates both feeding and energy expenditure (Hwa et al., 1999).

Porcine- and chicken-neuropeptide Y differ by only two amino acids (94% identity). Recently, all five presently known mammalian receptors in chicken were cloned (Larhammar et al., 2000). The amino acid identity is 85%, 85% and 77% for neuropeptide Y Y_1, Y_2 and Y_5 receptors, respectively, when the transmembrane regions are compared to their mammalian orthologues (Holmberg et al., 2000). Among neuropeptide Y receptors, the neuropeptide Y Y_4 receptor displays the lowest degree of identity between species where chicken neuropeptide Y Y_4 receptor has only 56–60% overall amino acid identity to neuropeptide Y Y_4 receptor from mammalians, compared to the neuropeptide Y Y_1, Y_2 and Y_5 receptors (Lundel et al., 2000). A partial chicken neuropeptide Y Y_6 receptor sequence deduced from polymerase chain reaction fragment has 65% identity to Y_6 from mouse and rabbit (human neuropeptide Y Y_6 receptor is a pseudogene) (Lundel et al., 2000).

Although affinities of several agonists at mammalian neuropeptide Y receptors are clarified, there is little information about feeding responses by several neuropeptide Y receptor agonists in the chick. The aim of this study is to elucidate which neuropeptide Y receptor agonists function in the central nervous system to stimulate feeding in the neonatal chick.

2. Materials and methods

2.1. Animals

Day-old male broiler chicks (Cobb) were purchased from a local hatchery (Mori Hatchery, Fukuoka, Japan). Birds were housed in a room with continuous lighting and temperature at 28 °C. The birds were given free access to a commercial starter diet (Toyohashi Feed and Mills, Aichi, Japan) and water, and were maintained in accordance with recommendations of the National Research Council (1985). Chicks were distributed into experimental groups based on their body weight, so that the average body weight was as uniform as possible among treatment groups. The experimental conditions such as room temperature, lighting, feeding conditions were based on those used by Furuse et al. (1997) in which neuropeptide Y was shown to stimulate feeding.

2.2. Peptide and intracerebroventricular (i.c.v.) infusion protocols

The birds were injected with 10 μl i.c.v. using a microsyringe according to the methods by Davis et al. (1979). Neuropeptide Y (porcine), [Leu^{31}, Pro^{34}]neuropeptide Y (porcine) and neuropeptide Y-(13–36) (porcine) were purchased from Peptide Institute (Osaka, Japan). Peptide YY (porcine) and pancreatic polypeptide (human) were purchased from Sigma (St. Louis, MO, USA). [D-Trp^{32}]neuropeptide Y (porcine) and pancreatic polypeptide (rat) were purchased from Peninsula Laboratories (Belmont, CA, USA). Peptides were dissolved in a 0.1% Evans Blue solution which was prepared in 0.85% saline. The doses of peptides applied in this study were based on those shown to be effective in mammals (Iyengar et al., 1999). At the end of the experiments, the birds were sacrificed with an overdose of pentobarbital, and the location of the injection site was verified. Data from individuals lacking dye in the lateral ventricle were deleted.

2.3. [Leu^{31}, Pro^{34}]neuropeptide Y

Birds 2 days of age were injected i.c.v. with 0, 94, 235 or 588 pmol of [Leu^{31}, Pro^{34}]neuropeptide Y, and food intake was monitored for 2 h. The numbers of birds used were: control, 10; 94 pmol, 8; 235 pmol, 8; and 588 pmol, 10, respectively.

2.4. Neuropeptide Y and [Leu^{31}, Pro^{34}]neuropeptide Y

Birds 3 days of age were injected i.c.v. with either 0, 59 or 118 pmol of neuropeptide Y or with either 59 or 118 pmol of [Leu^{31}, Pro^{34}]neuropeptide Y. Food intake recorded for 2 h post-injection. The numbers of birds used in the neuropeptide Y administration were: control, 7; 59 pmol, 7; and 118 pmol, 8 and in the [Leu^{31}, Pro^{34}]neuropeptide Y administration were: 59 pmol, 8; and 118 pmol, 7, respectively.

2.5. Neuropeptide Y and peptide YY

Birds 2 days of age were injected i.c.v. with three 0, 59 or 118 pmol of neuropeptide Y or either 59 or 118 pmol of peptide YY. Food intake was monitored for 2 h post-injection. The numbers of birds used in the neuropeptide Y administration were: control, 8; 59 pmol, 8; and 118 pmol, 8 and in the peptide YY administration were: 59 pmol, 8; and 118 pmol, 7, respectively.

2.6. Neuropeptide Y-(13–36)

Birds 2 days of age were injected i.c.v. with 0, 94, 235 or 588 pmol of neuropeptide Y-(13–36). Food intake was then measured through 2 h post-injection. The numbers of birds used were: control, 8; 94 pmol, 8; 235 pmol, 10; and 588 pmol, 7, respectively.

2.7. Human pancreatic polypeptide

Birds 1 day of age were injected i.c.v. route with 0, 147, 294 or 588 pmol of human pancreatic polypeptide.

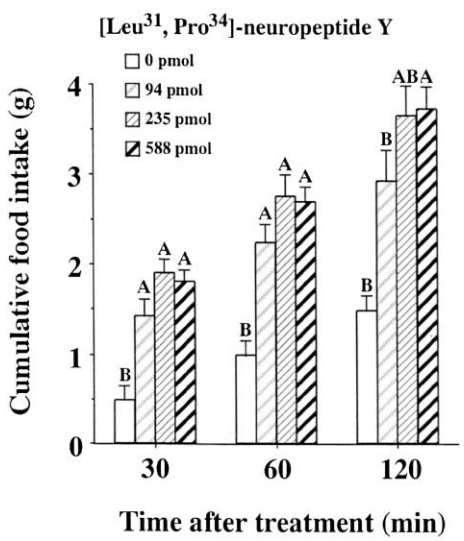

Fig. 1. Cumulative food intake of chicks administered saline or [Leu^{31}, Pro^{34}]neuropeptide Y (94, 235 or 588 pmol) intracerebroventricularly under ad libitum feeding conditions. Values are means ± S.E.M. Means without a common letter (A or B) at the same time are significantly different ($P < 0.05$). The number of birds used was; control, 10; 94 pmol, 8; 235 pmol, 8; and 588 pmol, 10.

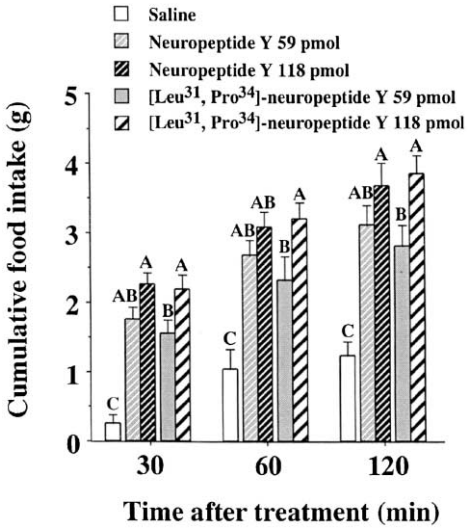

Fig. 2. Cumulative food intake of chicks administered saline, neuropeptide Y (59 or 118 pmol) or [Leu^{31}, Pro^{34}]neuropeptide Y (59 or 118 pmol) intracerebroventricularly under ad libitum feeding conditions. Values are means ± S.E.M. Means without a common letter (A, B or C) at the same time are significantly different ($P < 0.05$). The number of birds used was; control, 7; neuropeptide Y 59 pmol, 7; neuropeptide Y 118 pmol, 8; [Leu^{31}, Pro^{34}]neuropeptide Y 59 pmol, 8; and [Leu^{31}, Pro^{34}]neuropeptide Y 118 pmol, 7.

The numbers of birds used were: control, 9; 147 pmol, 8; 264 pmol, 10; and 588 pmol, 7, respectively.

2.8. Rat pancreatic polypeptide

Birds 2 days of age were injected i.c.v. with 0, 94, 235 or 588 pmol of rat pancreatic polypeptide. The numbers of birds used were: control, 10; 94 pmol, 9; 235 pmol, 8; and 588 pmol, 10, respectively.

2.9. [D-Trp^{32}]neuropeptide Y

Birds (2 days old) were injected i.c.v. route with 0, 94, 235 or 588 pmol of [D-Trp^{32}]neuropeptide Y. The numbers of birds used were: control, 10; 94 pmol, 9; 235 pmol, 8; and 588 pmol, 10, respectively.

2.10. Measuring of food intake

Food intake was determined at 30, 60 and 120 min by measuring the disappearance of diet from a pre-weighed feeder. The weight of feeders was weighed by using an electric digital balance of precision ± 1 mg.

2.11. Statistical analysis

Data were subjected to one-way analysis of variance by the General Linear Model procedure using a commercially available package (SAS Institute, 1985), and comparisons

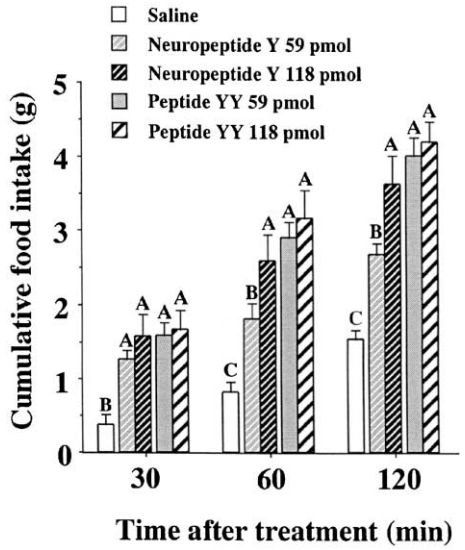

Fig. 3. Cumulative food intake of chicks administered saline, neuropeptide Y (59 or 118 pmol) or peptide YY (59 or 118 pmol) intracerebroventricularly under ad libitum feeding conditions. Values are means ± S.E.M. Means without a common letter (A, B or C) at the same time are significantly different ($P < 0.05$). The number of birds used was; control, 8; neuropeptide Y 59 pmol, 8; neuropeptide Y 118 pmol, 8; peptide YY 59 pmol, 8; and peptide YY 118 pmol, 7.

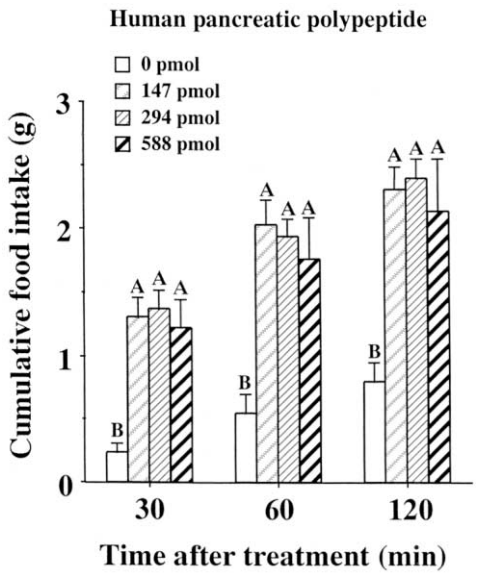

Fig. 5. Cumulative food intake of chicks administered saline or human pancreatic polypeptide (147, 294 or 588 pmol) intracerebroventricularly under ad libitum feeding conditions. Values are means ± S.E.M. Means without a common letter (A or B) at the same time are significantly different ($P < 0.05$). The number of birds used was; control, 9; 147 pmol, 8; 294 pmol, 10; and 588 pmol, 7.

between means were made using Duncan's multiple range test. The results are shown as the mean ± S.E.M.

3. Results

In the present study, the pharmacological effects of neuropeptide Y and related analogs on food consumption were characterized in the neonatal chick. Fig. 1 shows the effect of central injection of [Leu^{31}, Pro^{34}]neuropeptide Y on food intake of the neonatal chick. [Leu^{31}, Pro^{34}]neuropeptide Y stimulated food intake compared with the control. The orexigenic efficacy of neuropeptide Y and [Leu^{31}, Pro^{34}]neuropeptide Y is shown in Fig. 2. When compared with neuropeptide Y at equimolar doses, [Leu^{31}, Pro^{34}] neuropeptide Y was equally efficacious with neuropeptide Y.

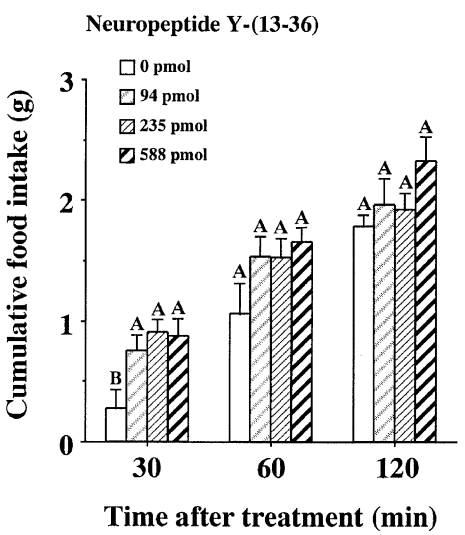

Fig. 4. Cumulative food intake of chicks administered saline or neuropeptide Y-(13–36) (94, 235 or 588 pmol) intracerebroventricularly under ad libitum feeding conditions. Values are means ± S.E.M. Means without a common letter (A or B) at the same time are significantly different ($P < 0.05$). The number of birds used was; control, 8; 94 pmol, 8; 235 pmol, 10; and 588 pmol, 7.

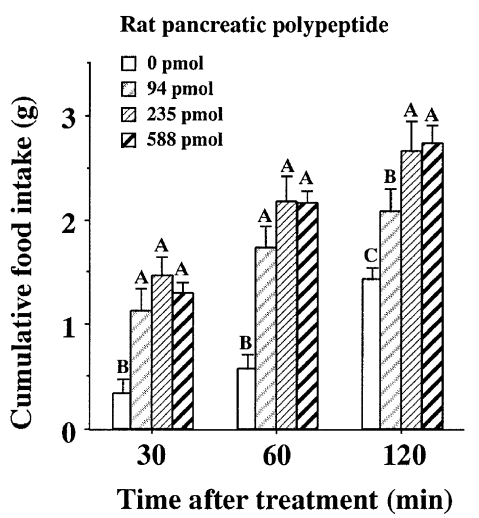

Fig. 6. Cumulative food intake of chicks administered saline or rat pancreatic polypeptide (94, 235 or 588 pmol) intracerebroventricularly under ad libitum feeding conditions. Values are means ± S.E.M. Means without a common letter (A, B or C) at the same time are significantly different ($P < 0.05$). The number of birds used was; control, 10; 94 pmol, 9; 235 pmol, 8; and 588 pmol, 10.

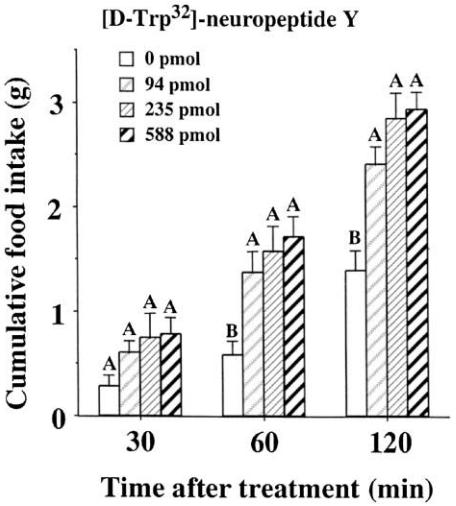

Fig. 7. Cumulative food intake of chicks administered saline or [D-Trp^{32}]neuropeptide Y (94, 235 or 588 pmol) intracerebroventricularly under ad libitum feeding conditions. Values are means ± S.E.M. Means without a common letter (A or B) at the same time are significantly different ($P < 0.05$). The number of birds used was; control, 10; 94 pmol, 9; 235 pmol, 10; and 588 pmol, 9.

Peptide YY appeared much more potent than neuropeptide Y in eliciting food consumption (Fig. 3). In contrast, neuropeptide Y-(13–36) weakly stimulated food consumption in a non-dose-dependent manner, and the effect was short-lived having disappeared by 60 min (Fig. 4). Both human pancreatic polypeptide (Fig. 5) and rat pancreatic polypeptide (Fig. 6) stimulated food consumption of the chick. As shown in Fig. 7, [D-Trp^{32}]neuropeptide Y promoted feeding of neonatal chicks at 60 and 120 min, but not at 30 min. This response was different from that of the other agonists since its effects were delayed relative to the other agonists.

4. Discussion

The chicken neuropeptide Y Y_4 receptor expressed in COS-7 cells binds porcine ^{125}I-peptide YY with high affinity and has a K_d value of 0.02 nM. Like all neuropeptide Y Y_4 receptors in mammals, it binds pancraetic polypeptide with high affinity, in the low picomolar range (Lundel et al., 2000). Chicken neuropeptide Y Y_2 and Y_5 receptors bind porcine peptide YY with $K_d = 25 \pm 2$ pM and $K_d = 113 \pm 10$ pM, respectively. In competition studies with porcine ^{125}I-peptide YY, the order of affinities to chicken neuropeptide Y Y_2 receptor are: porcine neuropeptide Y = chicken peptide YY > porcine neuropeptide Y-(2–36) > porcine neuropeptide Y-(13–36) > porcine [Leu^{31}, Pro^{34}]neuropeptide Y. Affinities to chicken neuropeptide Y Y_5 receptor are: porcine neuropeptide Y = porcine [Leu^{31}, Pro^{34}]neuropeptide Y = porcine neuropeptide Y-(3–36) = human pancreatic polypeptide > chicken peptide YY > porcine [D-Trp^{32}]neuropeptide Y = rat pancreatic polypeptide (Holmberg et al., 2000). Furthermore, porcine [Leu^{31}, Pro^{34}]neuropeptide Y, which binds poorly to mammalian neuropeptide Y Y_2 receptor, exhibited an unexpectedly high affinity for chicken (Salaneck et al., 2000).

The results (Figs. 1 and 2) suggest that [Leu^{31}, Pro^{34}]neuropeptide Y has a similar effect to neuropeptide Y. [Leu^{31}, Pro^{34}]neuropeptide Y has a high affinity to chicken neuropeptide Y Y_2 and Y_5 receptor (other receptors binding have not been clarified). Therefore, neuropeptide Y Y_2 and Y_5 receptors may regulate feeding behavior in chicken. However, i.c.v. injection of neuropeptide Y-(13–36), which has a high affinity to the chicken neuropeptide Y Y_2 receptor, stimulated food consumption at only 30 min, and the effect was weak (Fig. 4). The data indicate that the neuropeptide Y Y_2 receptor may not be as important receptor in mediating feeding in chicks as it is in rats and mice (Hwa et al., 1999; Iyengar et al., 1999). On the other hand, neuropeptide Y is a potent inhibitor of neurotransmitter release through the neuropeptide Y Y_2 receptor subtype in mammals (Walker et al., 1991). To authors' knowledge, this fact has not been confirmed in the chicken. The effect of neuropeptide Y-(13–36) on feeding for 30 min may imply the different mechanism of neurotransmitter release through the neuropeptide Y Y_2 receptor subtype between rodents and chicks.

Peptide YY has previously been shown to increase food intake in chicks (Kuenzel et al., 1987). Peptide YY was much more potent than neuropeptide Y in eliciting food consumption (Fig. 3). This result reflects some difference of affinity to neuropeptide Y receptors between neuropeptide Y and peptide YY. Central administration of human pancreatic polypeptide and rat pancreatic polypeptide increased food intake significantly (Figs. 5 and 6). In a similar experiment in rats, human pancreatic polypeptide induced a dose-dependent increase of feeding behavior, whereas rat pancreatic polypeptide did not cause any significant changes in food intake (Hwa et al., 1999). Human pancreatic polypeptide has high affinity to mammalian neuropeptide Y Y_4 and Y_5 receptors. On the other hand, rat pancreatic polypeptide binds only neuropeptide Y Y_4 receptor in mammalian. Therefore, mammalian neuropeptide Y Y_5 receptor is expected to mediate feeding response of neuropeptide Y in mammalian spices. However, similar to human pancreatic polypeptide, rat pancreatic polypeptide has a high affinity to neuropeptide Y Y_4 and Y_5 receptors in chickens (Holmberg et al., 2000). If the chicken neuropeptide Y Y_5 receptor mediates feeding behavior as well as the mammalian neuropeptide Y Y_5 receptor, this fact agrees with the results of i.c.v. injection of rat pancreatic polypeptide in the present study.

[D-Trp^{32}]neuropeptide Y stimulated food intake of neonatal chicks at 60 and 120 min, but not at 30 min (Fig. 7). Its delayed response is similar to that in mice in which [D-Trp^{32}]neuropeptide Y elicited a modest but significant increase in food intake 2 h after i.c.v. infusion (Hwa et al.,

1999). Compared with effects of rat pancreatic polypeptide and [D-Trp^{32}]neuropeptide Y, rat pancreatic polypeptide was more potent than [D-Trp^{32}]neuropeptide Y in feeding of chicks at 30 and 60 min. However, affinities of rat pancreatic polypeptide and [D-Trp^{32}]neuropeptide Y for chicken neuropeptide Y Y_5 receptor were equal (Holmberg et al., 2000). So, neuropeptide Y Y_5 receptor may mediate feeding response of chicks, but other neuropeptide Y receptors (include neuropeptide Y Y_4 receptor) may be involved in feeding behavior in the neonatal chick.

In conclusion, neuropeptide Y receptor agonists, except for neuropeptide Y-(13–36), are potent stimulators of food intake of the neonatal chick. This result reflects structural differences of neuropeptide Y receptor subtypes and/or differences in mechanism to stimulate feeding behavior between mammals and chickens. Study of binding properties of another neuropeptide Y receptor agonists and antagonists for neuropeptide Y receptors (Y_1–Y_6) will help to clarify what receptor mediates the orexigenic action of neuropeptide Y in the chicken brain.

Acknowledgements

This study was supported by grant-in-aid for scientific research from the Ministry of Education, Science and Culture, Japan and Uehara Memorial Foundation.

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