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Central administration of vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide differentially regulates energy metabolism in chicks

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Abstract

Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) are the members of the glucagon superfamily and bind to common receptors while PACAP also acts via the PACAP-specific receptor, PAC1. The aim of the present study was to investigate whether intracerebroventricular (ICV) injection of VIP and PACAP acts in a similar or different manner to affect body temperature and energy expenditure in the domestic chick. ICV injection of VIP did not significantly affect rectal temperature, but decreased energy expenditure. On the other hand, ICV injection of PACAP significantly increased both body temperature and energy expenditure. These specific actions of PACAP could be explained by an interaction with the PAC1 receptor, since they were partly, but not entirely, attenuated by PACAP (6–38), a PAC1 receptor antagonist. In addition, it was observed that central administration of both VIP and PACAP induced a reduction in respiratory quotient and increased plasma non-esterified fatty acid concentrations. This suggests that both peptides act centrally to regulate a catabolic response. In summary, brain VIP and PACAP both appear to exert generally catabolic effects on energy metabolism in the chick, but their influence on body temperature and glucose metabolism differs and their central effects do not appear to be mediated by the same receptors.

Keywords: Chicks; Energy expenditure; Intracerebroventricular injection; Pituitary adenylate cyclase-activating polypeptide; Plasma constituents; Rectal temperature; Vasoactive intestinal peptide

1. Introduction

Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) belong to the glucagon superfamily and bind to common receptors (Harmar et al., 1998). PACAP also binds to the specific PAC1 receptor (Harmar et al., 1998). These peptides regulate changes in physiological state through both peripheral and central pathways. Previous studies have revealed that central VIP and PACAP affect energy homeostasis in mammals. For example, intracerebroventricular (ICV) injection of PACAP inhibits feeding behavior of mice (Morley et al., 1992). VIP also exerts an anorexic effect in mammals (Woods et al., 1981). In addition, these peptides are involved in the control of body temperature and energy expenditure. Mice lacking the VPAC2 receptor, which is a common receptor for VIP and PACAP, showed an increase in basal metabolic rate when compared with their wild-type siblings (Asnicar et al., 2002). Moreover, since ICV injection of VIP decreases body temperature (following a slight increase in body temperature) in rats (Itoh and Hirota, 1982), central VIP appears to act as a hypothermic factor to decrease metabolic rate. On the other hand, ICV injection of PACAP increases body temperature in rats (Masuo et al., 1995; Pataki et al., 2000). In addition, mice lacking PACAP cannot survive in cold conditions (Gray et al., 2002), suggesting that PACAP acts as a hyperthermic factor and increases metabolic rate. These facts clearly demonstrate that although these peptides share a

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common receptor, they exert different physiological effects in mammals.

We have reported that both VIP and PACAP inhibit feeding behavior in chicks when administered centrally (Tachibana et al., 2003a), but induce their anorexigenic effects through different mechanisms (Tachibana et al., 2003b). We have demonstrated an interaction of both peptides with corticotropin-releasing factor (CRF) neurons (Tachibana et al., 2004b) and central CRF increases body temperature (Tachibana et al., 2004a) and energy expenditure (Tachibana et al., 2006) in chicks. These results suggest that VIP and PACAP are involved in the maintenance of energy balance by the brain. However, it is possible that the two peptides influence energy homeostasis in different ways. Therefore, in the present study, we investigated whether ICV injections of VIP and PACAP exerted similar or different effects on body temperature, energy expenditure, and respiratory quotient (RQ) in the chick. To investigate a possible influence of the peptides on glucose and lipid metabolism, we measured plasma concentrations of glucose (GLU), triacylglycerol (TG) and non-esterified fatty acids (NEFA) after ICV injection of VIP and PACAP. Finally, we determined the possible involvement of the PAC1 receptor in mediating the central effects of PACAP.

2. Materials and methods

2.1. Animals

Day-old male layer chicks (*Gallus gallus*, Julia strain) were purchased from a local hatchery (Murata Hatchery, Fukuoka, Japan) and kept in a room at 30 °C under continuous lighting. The birds were allowed free access to a commercial diet (Toyohashi Feed and Mills Co. Ltd., Aichi, Japan) and water except as noted elsewhere. Experimental procedures followed the guidance for Animal Experiments in Faculty of Agriculture and in the Graduate Course of Kyusyu University and the Law (No.105) and Notification (No.6) of the Government.

2.2. ICV injection

Rat VIP, rat PACAP-38 and PACAP (6–38) (all purchased from Peptide Institute, Osaka, Japan) were dissolved in a 0.1% Evans Blue solution prepared in a saline. The physiological action of mammalian VIP is weaker than that of chicken VIP in chicks (Nowak and Kuba, 2001). However, since the mammalian VIP could inhibit feeding behavior (Tachibana et al., 2003a,b, 2004b) and increase corticosterone release in chicks (Tachibana et al., 2004b) as shown in mammals, we decided that mammalian VIP is useful to investigate the effect of VIP and used mammalian VIP for the present study. The control group was injected with the same volume of this Evans Blue solution. The injection volume was 10 μl in all experiments.

ICV injection was conducted according to the method of Davis et al. (1979). Briefly, the head of the chick was inserted in an acrylic device which restrained the head and positioned a hole in a plate to lie immediately above the left lateral ventricle. A microsyringe was then inserted into the left lateral ventricle through the hole in the plate and the drug was injected. This method does not appear to induce physiological stress in the chick because ICV injection of saline solution, which was used as the control group in the present study, did not affect feeding behavior (Furuse et al., 1999) and corticosterone release (Saito et al., 2005) when compared to non-injected birds. Therefore, we did not anesthetize chicks for the injection and they were free to move and eat immediately after the injection. At the end of each experiment, chicks were sacrificed with an intraperitoneal overdose of sodium pentobarbital. Confirmation of drug injection was made by observation of the presence of Evans Blue dye in the lateral ventricle. The results obtained from chicks which did not have Evans Blue dye in the lateral ventricle were not used.

2.3. Experiment 1: effects of VIP and PACAP on rectal temperature

To determine rectal temperature, a 19-mm stainless sensor connected to a recorder (Thermalert TH-5, Physitemp Instruments Inc., New Jersey, USA) was inserted into the rectum. Briefly, each chick was removed from the cage and fixed with hand softly. The sensor was then inserted into the cloaca at a depth of 19 mm. The measurement of the rectal temperature was finished within 5 s, the chick was then returned to the cage.

After the measurement of the basal rectal temperature, each chick (6 days old) was ICV injected with 0 (control), 47 or 188 pmol VIP. The rectal temperature was then measured at 30 and 60 min after the injection. Food and water were not given to the chicks during the post-injection period. The number of chicks in each group was as follows: 0 pmol, 6; 47 pmol, 8; and 188 pmol, 6.

In the PACAP study, 5-day-old chicks were used and the experimental treatment was the same as used for the VIP study. The number of chicks in each group was as follows: 0 pmol, 7; 47 pmol, 8; and 188 pmol, 9.

2.4. Experiment 2: effects of VIP and PACAP on energy expenditure and RQ

To investigate energy expenditure, oxygen (O_2) consumption, carbon dioxide (CO_2) production and RQ were measured using an open-circuit calorimeter system (MK-5000RQ, Muromachi Kikai Co. Ltd., Tokyo, Japan). For the measurements, an acrylic chamber (150 mm × 150 mm × 150 mm) with a stainless steel grid floor was used. Fresh atmospheric air was drawn at a rate of 500 ml/min and then passed through O_2 and CO_2 detectors (MM202R, Muromachi Kikai Co., Ltd., Tokyo, Japan). The concentrations of these gases were recorded every 3 min. The analyzer was calibrated using primary gas standards of high purity (Sumitomo Seika Chemicals Co. Ltd., Osaka, Japan) every 1 h. Energy expenditure was calculated by the equation of Romijn and Lokhorst (1961) as follows: energy expenditure (kcal/min) = the volume of O_2 consumed (ml/