The Investigation of the Relations between Insulin-liked Growth Factor-I and Body Weight and between Insulin-liked Growth Factor-I and Sex in Young Cats

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Abstract

High plasma IGF-I concentration has been found in large breed young dogs, but not in young cats. The objective of this study was to investigate the relation between the concentration of IGF-I and body weight in both male and female cats at young age. In this study, the plasma IGF-I concentrations and body weight in 4 female and 4 male cats at 5, 11, 17 and 21 months old were examined. No significant difference in the body weight between the female and male kittens (3.1 ± 0.2 kg and 3.2 ± 0.3 kg) at 5 months old was found, but at 11, 17 and 21 months old (5.3 ± 0.2 kg, 5.3 ± 0.4 kg, 5.4 ± 0.2 kg) the male cats had significantly higher body weight ($p<0.01$) than the female cats (3.1 ± 0.3 kg, 3.3 ± 0.2 kg, 3.4 ± 0.3 kg). The IGF-1 concentration in the male cats (945 ± 41 ng/ml) was significantly higher ($p<0.05$) than that in the female cats (520 ± 39 ng/ml) at the age of 5 months. At 11 and,17 months old, but not at 21 months old, the mean plasma IGF-1 levels (772 ± 122 and 713 ± 33 ng/ml) in the male cats were significantly higher than those in the female cats (323 ± 77 and 197 ± 36 ng/ml) ($p<0.05$). In conclusion, the results of this study indicated that there were relations between IGF-I and body weight and between IGF-I and sex in young cats. Moreover, the diversity of plasma IGF-1 concentrations in male and female cats can be found at the age of 5 months and over.

Keywords: body weight, cats, IGF-I, sex

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บทคัดย่อ

การศึกษาความสัมพันธ์ระหว่าง Insulin-liked Growth Factor-I และน้ำหนักตัวและเพศในลูกแมว

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ค่าความเข้มข้นพลาสมา IGF-I   มีรายงานการตรวจพบในระดับสูงในลูกสุนัขพันธุ์ใหญ่ แต่ไม่พบในลูกแมว วัตถุประสงค์ของการศึกษาในครั้งนี้ เพื่อหาความสัมพันธ์ระหว่างค่าความเข้มข้นพลาสมา IGF-I และน้ำหนักตัวในลูกแมวทั้ง 2 เพศ โดยทำการตรวจค่าความเข้มข้นพลาสมา IGF-I ในแมวเพศเมียและเพศผู้ จำนวนเพศละ 4 ตัว ที่ช่วงอายุ 5 11 17 และ 21 เดือน ตามลำดับ ผลการศึกษาพบว่า น้ำหนักตัวของลูกแมวเพศผู้และเมีย มีค่าเท่ากับ 3.1±0.2 กก. และ 3.2±0.3 กก. ที่ช่วงอายุ 5 เดือน ซึ่งไม่มีความแตกต่างอย่างมีนัยสำคัญ ในขณะที่แมวเพศผู้ช่วงอายุ 11 17 และ 21 เดือนมีค่าน้ำหนักตัวเท่ากับ 5.3±0.2 กก. 5.3±0.4 กก. และ 5.4±0.2 กก. ซึ่งพบว่าค่าดังกล่าว สูงกว่าแมวเพศเมีย ซึ่งมีค่าเท่ากับ 3.1±0.3 กก. 3.3±0.2 กก. และ 3.4±0.3 กก. อย่างมีนัยสำคัญทางสถิติ($p<0.01$) ในช่วงอายุเดียวกัน ค่าความเข้มข้นพลาสมา IGF-I ในแมวเพศผู้ (945±41 ng/ml) มีค่าสูงแตกต่างอย่างมีนัยสำคัญ ($p<0.05$) กว่าแมวเพศเมีย (520±39 ng/ml) ที่ช่วงอายุ 5 เดือน ที่ช่วงอายุ 11 และ17 เดือน ยกเว้น 21 เดือน ค่าเฉลี่ยความเข้มข้นพลาสมา IGF-I ในแมวเพศผู้ มีค่า (772±122 และ 713±33 ng/ml) ซึ่งมีค่าสูงกว่าแมวเพศเมีย อย่างมีนัยสำคัญทางสถิติ (323±77 และ 197±36 ng/ml) ($p<0.05$) สรุปผลการศึกษาพบว่า มีความสัมพันธ์ระหว่างค่าความเข้มข้นพลาสมา IGF-I และน้ำหนักตัว และเพศในลูกแมว ซึ่งแสดงผลอย่างชัดเจนในช่วงแมวอายุมากกว่า 5 เดือนขึ้นไป

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Introduction

The plasma concentration of insulin-like growth factor-1 (IGF-1) is regulated by growth hormone (GH), which stimulates IGF-1 synthesis in the liver and other tissues. IGF-1 participates in the growth and function of almost every organ in the body (Müller et al., 1999; Kitiyanant et al., 2003). There is a complex interplay in the metabolic actions of GH and IGF-1. In circulation, IGF-1 is transported in the serum bound to specific high-affinity binding proteins (IGFBP-1 to IGFBP-6) mainly produced in the liver. Most of the circulating IGF-1 (more than 90–95%) is bound to IGF-binding protein-3 (IGFBP-3) in a ternary complex with an acid-labile subunit (ALS) (Lin-Su and Wajnrajch, 2002; Kitiyanant et al., 2003; Mak et al., 2008). Some studies have been documented that tissues that determine the regulation of GH and IGF-1 peptide and receptors may be controlled by sex steroid. For example, in rats, estradiol can induce the synthesis of IGF-1 and its receptor and alter the availability of selected IGFBPs in the central nervous system (CNS), pituitary gland, ovary, breast, uterus, bone, and pre-adipocytes while inhibiting IGF-1 production by the liver. Estradiol can also stimulate the hepatic (subtype 1) GH receptor, but represses in the hypothalamus. Testosterone and non-aromatizable androgens induce IGF-1 peptide in bone, muscle, and skin, but suppress type I IGF receptor in fat (Veldhuis et al., 2006). Besides the regulation of IGF-1 by the sex steroids, the concentrations of IGF-1 might also be an important maturation process in animals. In fact, puberty is an endocrinologically transitional process that marks progression from childhood to adulthood. The concurrent activation of the somatotropic and gonadotropic axes is a hallmark of this physiological transition (Veldhuis et al., 1997). In human, it has been reported that IGF-1 concentration increases with age in prepubertal boys (Guercio et al., 2002) and girls (Guercio et al., 2003). In fact, in dogs body size is associated with the level of IGF-I (Eigenmann et al., 1988). For dogs, their body sizes are associated with the level of IGF-I (Eigenmann et al., 1988). Therefore, large breed dogs present a higher concentration of

IGF-I in comparison with small breed dog at a young age (Favier et al., 2001). As for cats, IGF-I concentrations were detected in cats ranging from four to sixteen years old, but no significant differences in the concentration between the sexes were shown (Reusch et al., 2006). Moreover, information concerning the differences in the concentration of IGF-1 between male and female cats less than two years old is limited. Thus, the aim of this study was to investigate the concentration of IGF-I and its relation to body weight in both male and female cats at a young age.

Materials and Methods

Animals: Eight healthy mixed breed cats including 4 males and 4 females were used in this study. The cats were purchased at 2 months of age from a cat shelter in Taichung, Taiwan. They were raised together in a bright (12 hours per day) and temperature (25-28°C) controlled room. The cats were fed with standard commercial dry food and provide with water *ad libitum*. The cats used in this study were 5, 11, 17 and 21 months old. All blood drawing was carried out in conscious animals after overnight fast. The study was approved by Affidavit of Approval of Animal use Protocol, National Chung Hsing University.

Blood sampling for IGF-1 measurement: The blood samples for IGF-1 were collected from the cephalic vein of cats 5, 11, 17 and 21 months old. The collected blood samples were immediately transferred to EDTA-coated tubes, and chilled at 4°C. Plasma was separated by centrifuge at 1000 x g for 10 minutes, thereafter they were transferred to tubes and stored at -70°C until IGF-1 determination. Plasma IGF-1 was measured by two-site radioimmunometric assay (IRMA) (ACTIVE® Non-Extraction IGF-1 IRMA DSL-2800). The minimum concentration of IGF-1 that could be detected was 2.06 ng/ml. The intra- and inter coefficients of variance (CVs) for GH assay were 7.0 and 7.4%, respectively.

Statistical analysis: Values are presented as mean ± standard error of mean (SEM) and statistically analyzed using the SigmaPlot software version 9.0. The change of plasma hormone levels was tested by Analysis of variance (one-way ANOVA) using SAS version 9.1 software (SAS institute, Inc., Cary, NC). The significance of the difference between two means was tested using Mann-Whitney U test (SigmaPlot® 9.0). A *p* value of <0.05 was considered to be significant.

Table 1 Body weight (kg) of cats at different ages.

	5 months	11months	17months	21months
Female	3.7	3.7	3.9	4.2
	2.9	2.9	3.2	3.3
	2.8	3.4	3.2	3.3
	2.8	2.4	2.7	2.6
Mean±SEM	3.1±0.2	3.1±0.3	3.3±0.2	3.4±0.3
Male	3.9	5.2	5.1	5.2
	2.8	5.8	6.3	5.9
	2.8	5.0	4.6	5.1
	3.3	5.0	5.0	5.3
Mean±SEM	3.2±0.3	5.3±0.2	5.3±0.4	5.4±0.2

Results and Discussion

The individual and average body weights of the cats age 5, 11, 17 and 21months old are shown in Table 1. There was no significant difference in body weight between the female and male kittens (3.1±0.2 kg and 3.2±0.3 kg) at 5 months old (Fig. 1). The body weight of the male cats at the age of 11, 17 and 21 months old (5.3±0.2 kg, 5.3±0.4 kg, 5.4±0.2 kg) was significantly higher (*p*<0.05) than that of the female cats (3.1±0.3 kg, 3.3±0.2 kg, 3.4±0.3 kg) (Fig. 1).

The mean plasma concentrations of IGF-1 in cats at the age of 5, 11, 17 and 21 months are shown in Table 2. The mean plasma IGF-1 concentrations in the male cats were significantly higher than those in the female cats at 5, 11 and 17 months old (Fig. 2). In male cats, the mean plasma IGF-1 at 5 months old (945±41 ng/ml) was significantly higher (*p*<0.05) than at 17 and 21 months old (713±33 and 648±79 ng/ml) (Fig. 3). In female cats, the basal plasma IGF-1 level at 5 months old (520±39 ng/ml) was significantly higher (*p*<0.05) than that at 17 months old (197±36 ng/ml), but did not differ significantly at the age of 11
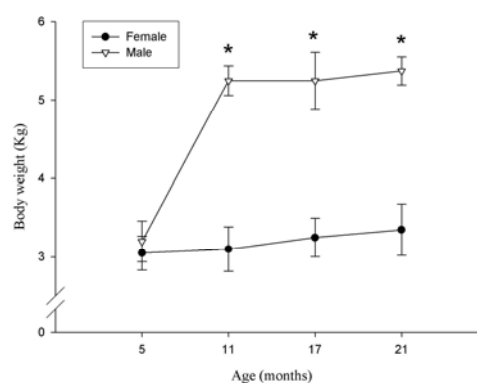

Figure 1 The body weight (kg) of the male and female cats at the age of 5 months, 11 months, 17 months and 21 months * indicates significant difference between male and female cats at the same age.
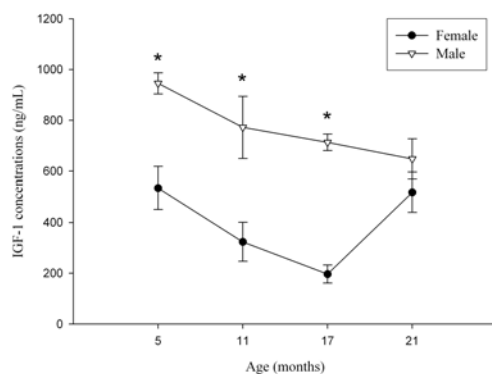
Figure 2 The concentrations (ng/ml) of IGF-1 in the male and female cats at the age of 5 months, 11 months, 17 months and 21 months. * indicates significant difference between the male and female cats of the same age.

Table 2 Basal plasma IGF-1 concentration (ng/ml) of cat at different ages.

	5 months	11months	17months	21months
Female	547	467	277	657
	451	203	130	473
	463	445	236	316
	619	180	144	627
Mean±SEM	535±84	772±122	713±33	648±79
Male	1057	684.5	779.5	574
	886	873.5	712	642
	880	481	625	506
	959	1049	736	870
Mean±SEM	945±41	772±122	713±33	648±79

and 21 months (323±77 and 518±79 ng/ml). The highest mean plasma IGF-1 concentrations were found at the age of 5 months after which it decreased with age. This might be associated with the lack of gonadal hormones. In fact, the first heat in queens can be as early as 4 or as late as 21 months depending on the breed (Jemmett and Evans, 1977). The concentrations of IGF-I can decrease by the effect of gonadal hormone. For example, IGF-1 concentrations increase significantly after castration in male cats (Martin et al., 2006), while oestrogen can attenuate GH action by reducing IGF-1 production (Mauras et al., 2006). However, the concentration of IGF-I increases as age increases in prepubertal and pubertal boys and girls (Guercio et al., 2002; Guercio et al., 2003). It is suggested that IGF-1 is able to stimulate proliferation in Leydig cells (Colón et al., 2007) and maturation of oocytes (Kitiyanant et al., 2003). Thus, the elevated concentrations of IGF-I observed at the age of 5 month old in kittens in this study might be an important maturation process for puberty in cats.

The mean concentrations of IGF-1 of 21 month-old female cats (518±79 ng/ml) was significantly higher ($p<0.05$) than that of 17 month-old female cats (197±36 ng/ml) (Fig. 4). The mean plasma IGF-1 level in the male cats was significantly higher than in the female cats at almost all ages in this study, except for the 21-month old group. This may be ascribed to the effect of sex steroids. After puberty, sex steroids can modulate IGF-1 secretion. In male cats, testosterone mediates GH action at the hypothalamic level by GHRH increased GH secretion with acromegalic increase in IGF-I level. In female cats, oestrogen attenuates GH action by reducing IGF-1 (Meinhardt and Ho, 2006). Furthermore, the production of IGF-1 may be associated with the secretory patterns of GH. In fact, the different GH secretory patterns have been reported in different genders (Veldhuis et al., 2000). Therefore, the higher IGF-1 concentration noted in 5 month old cats might be due to the high GH secretory burst mass. The elevated IGF-1 concentration in the male cats compared to female cats at a young age may indicate a different sensitivity of IGF-1 response to GH. Indeed, in humans, males experience a higher
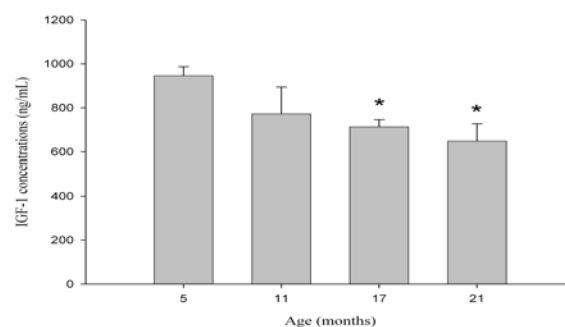

Figure 3 The mean concentrations of plasma IGF-1 in the male cats at the age of 5 months, 11 months, 17 months and 21 months. * indicates significant difference at 17 and 21 months old compared to 5 months old.
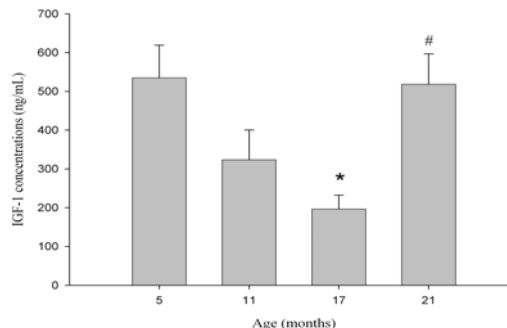

Figure 4 The mean concentrations of plasma IGF-1 in the female cats at the age of 5 months, 11 months, 17 months and 21 months. * indicates significant difference at 17 months old compared to 5 months old; # indicates significant difference at 17 months old compared to 21 months old.

response of IGF-1 to GH treatment (Mauras et al., 2007). Taken together; it may explain the result of this study, which showed higher IGF-1 concentrations in 5 month-old cats and a decrease in older age. To our knowledge, the gender diversity of plasma IGF-1 from 5 months old in cats has not been previously reported.

At 21 months old, the basal plasma IGF-1 level of the female cats was elevated when compared with that at 11 months old. It has been reported that elevated plasma IGF-1 was observed 2 days before behavioral estrous in goats (Hashizume et al., 2000). Thus, the elevated IGF-1 concentration at the age of 21 months in this study may be related to the effect of

sex steroids. Actually, the effect of oestrogen on the secretion of IGF-1 is still controversial. For example, in humans, high oestrogen concentration in the portal circulation impairs hepatic IGF-1 (Lin-Su and Wajnrajch, 2002; Moyano and Rotwein, 2004; Reusch et al., 2006), but in rats, oestradiol induces synthesis of IGF-1 and its receptors in such a way that it alters the availability of selected IGFBPs in the central nervous system (CNS), pituitary gland, ovary, breast, uterus, bone, and preadipocytes while inhibiting IGF-1 production by the liver (Veldhuis et al., 2006). IGF-1 is localized in the endometrial stroma and underlying myometrium, and its expression at both the mRNA and protein levels is shown to increase during the proliferative phase of menstrual cycle and in response to oestrogen in experiment animals. Several evidences have indicated that oestrogen is a key stimulator of IGF-1 gene and protein expression in the uterus (Moyano and Rotwein, 2004).

In conclusion, the difference of basal plasma IGF-1 level between sexes could be observed in cats since the age of 5 months, and male cats had significantly higher mean plasma IGF-1 levels than female cats. Thus, the relations between IGF-I and body weight and between IGF-I and sex in young cats and the differences in plasma IGF-I levels can be seen in the male and female cats at the age of 5 months and over.

Acknowledgements

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