The usefulness of somatotroph-specific aryl hydrocarbon receptor interacting protein knock out (sAIPKO) mice in developing therapeutics for GH secreting pituitary adenoma

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The usefulness of somatotroph-specific aryl hydrocarbon receptor interacting protein knock out (sAIPKO) mice in developing therapeutics for GH secreting pituitary adenoma

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ABSTRACT

The usefulness of somatotroph-specific aryl hydrocarbon receptor interacting protein knock out (sAIPKO) mice in developing therapeutics for GH secreting pituitary adenoma.

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(Directed by Professor Eun Jig Lee)

Acromegaly results from the chronic hypersecretion of GH, which primarily originates from GH secreting pituitary adenoma. Although transsphenoidaladenomectomy is the treatment of choice, some patients do not achieve biochemical remission after surgery and require medical treatment. However, there are not many available drugs due to the limitations of GH-secreting pituitary adenoma which include the poorly understood pathogenesis and lack of a proper animal model. Recently, Igenerated an animal model that develops GH secreting pituitary adenoma, which has the deletion of the aryl hydrocarbon receptor interacting protein (AIP) in somatotroph. To investigate the usefulness of somatotroph-specific AIP knock out (sAIPKO) mice in developing therapeutics for GH secreting pituitary

adenoma, I evaluated the biochemical effects of somatostatin analogs on sAIPKO mice. I generated sAIPKO mice using a Cre-loxp strategy.TwelvemalesAIPKO mice were assessed. The mice received a subcutaneous injection of octreotideLARorpasireotide LAR. Imeasured serum IGF-1 levels, body weight and blood glucose levels three times a month. There were significant decreases in serum IGF-1 levels in the pasireotide group. However, serum IGF-1 levels intheoctreotide group showed a decreasing trend, although it was not statistically significant. Body weight in the pasireotide group significantly decreased on the 14^{th} day, not on the 28^{th} day while there was no significant change in the octreotide group. Blood glucose levels in the pasireotide group increased significantly on 28^{th}day.Pasireotide which is a multireceptor targeted somatostatin analog, had stronger inhibitory effects on biochemical activity in sAIPKO mice suggesting that this mouse model represent more aggressive GH secreting pituitary adenoma. Thus, this mouse model will be useful for drug development and efficacy evaluation in GH secreting pituitary adenoma.

Key words: Acromegaly, Aryl Hydrocarbon Receptor Interacting Protein, Somatostatin Analog

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I. INTRODUCTION

Acromegaly is characterized by chronic hypersecretion of growth hormone(GH), which primarily originates from a GH-secreting pituitary adenoma and induces the synthesis of insulin-like growth factor 1 (IGF-1). Elevated GH and IGF-1 levels cause metabolic dysfunction and somatic growth, resulting in significant morbidity and mortality for patients with acromegaly. As decreasing GH to <2.5ug/L and IGF-1 to normal levels significantly reduces mortality, the main treatment goal for acromegaly

is to control GH and IGF-1 levels. Additional goals are to reduce tumor size, preserve pituitary function and prevent recurrence.[1-6]

First-line treatment is usually transsphenoidal surgery; however, cure rates decrease with increasing tumor size, extrasellar extension, and cavernous sinus invasion[7], and most patients with a macroadenoma require postsurgical medical treatment to achieve disease control.[2] Long-acting somatostatin analogs are the cornerstone of medical therapy for acromegaly.[8-10] However, many patients with acromegaly do not achieve biochemical control with the currently available somatostatin analogs.[11]

Pasireotide(SOM230) is a multireceptor-targeted somatostatin analog with high binding affinity for SSTR1, 2, 3 and SSTR5, including a 39- and 30-fold higher binding affinity for SSTR5 and SSTR1, respectively, than octreotide. Pasireotide showed a stronger inhibitory effect than octreotide on the secretion of GH, insulin-like growth factor 1 (IGF1), ACTH, and corticosterone in animal models, suggesting that pasireotide has the potential to be an effective therapy in patients with active acromegaly and Cushing's disease who are not responsive to octreotide.[12,13]

Germline mutations in the aryl hydrocarbon receptor interacting protein(AIP) gene have been found to occur in some patients with familial isolated pituitary adenoma (FIPA) and in sporadic young-onset pituitary adenomas.[14-18]Patients with AIP mutation are typically diagnosed with GH-secreting pituitary tumors (somatotropinomas, ~80% of cases) that cause acromegaly or gigantism.[19,20] These

tumors tend to be diagnosed at a younger age and are larger and more aggressive, and the somatotroph adenomas do not appear to respond well to somatostatin analogs.[14-18]

AIP has properties consistent with a tumor suppressor gene, with loss of heterozygosity observed in pituitary tumor samples and *in vitro* data showing that wild-type AIP attenuates cell proliferation, whereas mutant AIP loses this effect and AIP knockdown give rise to increased cell proliferation.[16,21]

There are not many available drugs due to the limitations of GH-secreting pituitary adenoma, which include the poorly understood pathogenesis and lack of proper animal model. For this reason, Irecently developed the animal model for GH-secreting pituitary adenoma, which has the deletion of aryl hydrocarbon receptor interacting protein(AIP) in somatotroph. To investigate the usefulness of somatotroph-specific AIP knock out (sAIPKO) mice in developing therapeutics for GH-secreting pituitary adenoma, I evaluated the effects of somatostatin analogs on the mice.

II. MATERIALS AND METHODS

1. Compounds and formulations

OctreotideLAR, pasireotide LAR and the appropriate vehicles for thosewas provided by NovartisPharma AG (Basel, Switzerland). Octreotide LAR (320mg/kg, monthly dose) and Pasireotide LAR (320mg/kg, monthly dose) were reconstituted with the appropriate vehicles and rapidly administeredsubcutaneously to the mice of each group according to the manufacturer's details provided by Novartis.An IGF-1 (insulin like growth factor-1) enzyme-linked immunosorbent assay (ELISA) kit was purchased from Abcam plc. (Cambridge, MA, USA).

2. Animals and treatments

I recently generated the mice which has the deletion of aryl hydrocarbon receptor interacting protein(AIP) in somatotroph**.** Mice lacking the AIP gene in pituitary somatotrophs were created by crossing mice with loxp sites flanking exons 5-7 of the AIP gene (AIP $^{lox/lox}$)with transgenic mice expressing the Cre-recombinase under control of the rat growth hormone (GH) promotor (rGHp-Cre^{tg}). The targeted deletion of exons 5-7 of the AIP gene leads to deletion of the tetratricopeptide repeat (TPR) domains, an area involved in protein-protein interactions, and a region encompassing

a hot spot mutation site in the corresponding human genome. First, I measured body weight, blood glucose levels and serum IGF-1 levels to group twelve male mice to three groups equally according to them; control (n=4), octreotide-treated group (n=4), pasireotide-treated group (n=4). I collected blood from the mice by retroorbital sinus-plexus sampling and measured the blood glucose levels by a glucometer (ARKRAY Factory, Inc., Kyoto, Japan). I also centrifuged it to obtain blood serum and measured serum IGF-1 levels by using IGF-1 mouse ELISA kit.After grouping, I injected carefully prepared octreotide LAR and pasireotide LAR into the back of the mice once a month and checked the changes in body weight, blood glucose levels, and serum IGF-1 levels for each group.

3. IGF-1 mouse ELISA

The blood serum is collected on 14^{th} and 28^{th}day in addition to the first day and serum IGF-1 levels were determined using a competitive binding IGF-1 mouse ELISA kit according to the manufacturer's instructions. The absorbance at 450 nm was measured and the serum IGF-1 levels for each sample were calculated using a standard curve generated with mouse IGF-1 reference solutions in the kit. The average of triplicate assays was calculated.

4. Statistical analysis

Statistical analysis was performed by using Statistical Package for the Social Sciences software (IBM Corp., version 21, 1989-2012). Data with normal distribution were expressed as mean± SD. Paired *t*-test was used to compare serum IGF-1 levels before and after the drug treatment for each group. One-way ANOVA test was used to compare the baseline characteristics. Statistical significance was assigned for $P < 0.05$.

III. RESULTS

1. Baseline characteristics of the sAIPKO mice

I used twelve male sAIPKO mice to evaluate the biochemical effects of somatostatin analogs in vivo. Their mean age is 61.7± 12.8 weeks. Igroupedthe mice to three groups; control, octreotide-treated group and pasireotide-treated group. As expected, there is no significant difference in the baseline characteristics between the three groups (Table 1).

Table 1. Baseline characteristics of the mice in the study

	Control (n=4)	Octreotide (n=4)	Pasireotide (n=4)	p value†
Age (wks)	**60.4±13.2**	**65.8±11.1**	**58.5±16.3**	**0.750**
Body weight (kg)	**35.8±4.1**	**36.4±4.0**	**38.5±3.5**	**0.604**
Plasma Glucose (mg/dl)	**170.3±25.7**	**137.5±34.0**	**163.8±16.8**	**0.233**
Serum IGF-1 (ng/ml)	**107.1±43.9**	**98.1±20.6**	**119.2±29.9**	**0.674**

IGF-1, Insulin-like growth factor-1

†: p value was measured by one-way ANOVA test

2. The biochemical effects of somatostatin analogs

On both the 14th and 28th days, there were significant decreases in serum IGF-1 levels in the pasireotide-treated group (p=0.016, p=0.008, respectively). However, serum IGF-1 levels in the octreotide-treated group showed a decreasing trend, although it was not statistically significant (Figure 1). Body weight in the pasireotide-treated group significantly decreased on the 14th day (p=0.048), not on the 28th day while there was no significant change in the octreotide-treated group(Figure 2). There was no significant change of blood glucose levels in the pasireotide-treated group on the 14th day. However, blood glucose levels increased significantly on the 28th day (p=0.027) in comparison with the 14th day. In contrast, there was no significant change of blood glucose levels in the octreotide-treated group (Figure 3).

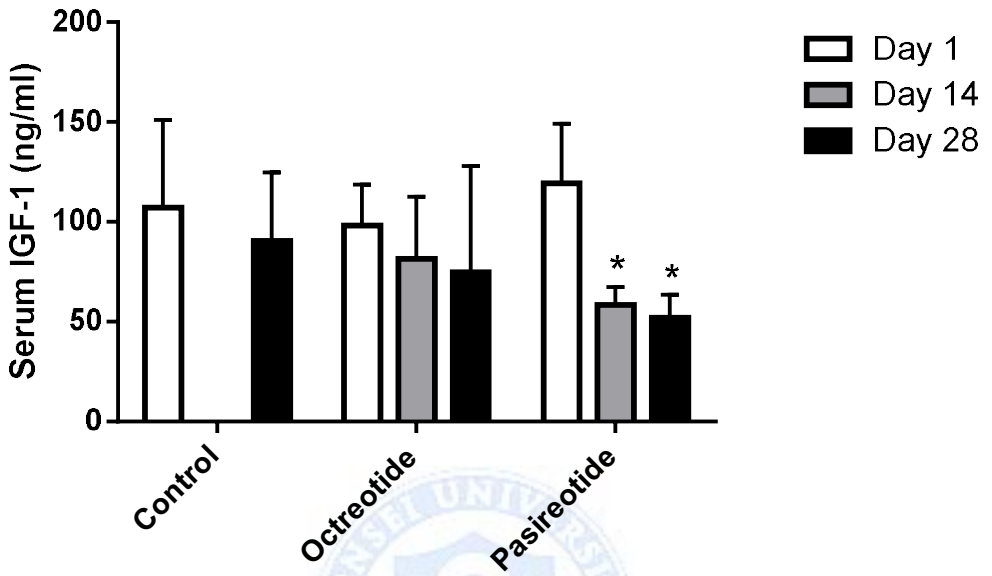

Figure 1. The changes in serum IGF-1 levels.Pasireotide LAR (320mg/kg) and octreotide LAR (320mg/kg) were injected subcutaneously once a month to the mice for each group. Serum IGF-1 levels were measured using ELISA kit. Data are expressed as mean±SD (n=4). *P<0.05 vs. before the treatement of somatostatin analogs.

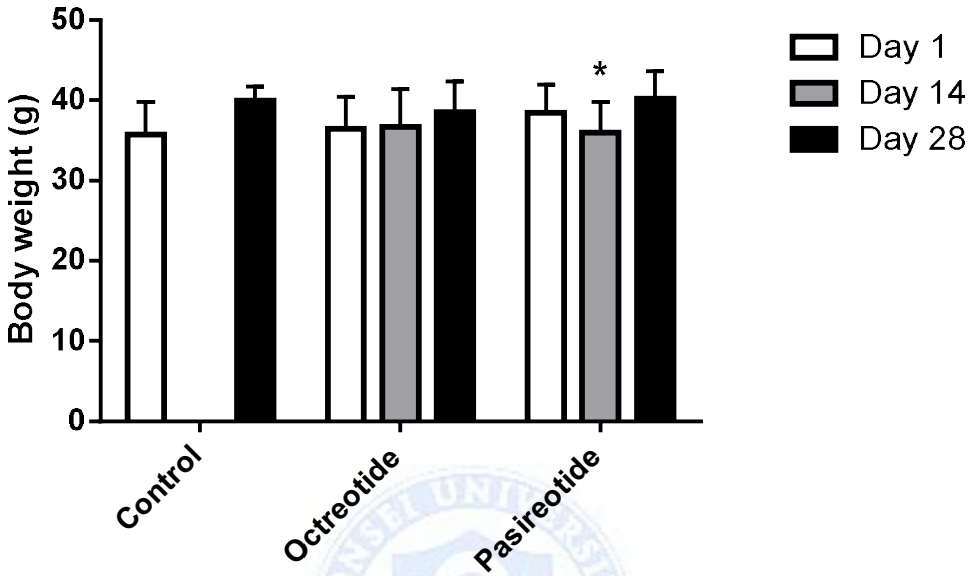

Figure 2. The changes in body weight. Pasireotide LAR (320mg/kg) and octreotide LAR (320mg/kg) were injected subcutaneously once a month to the mice for each group.Data are expressed as mean±SD (n=4). *P<0.05 vs. before the treatement of somatostatin analogs.

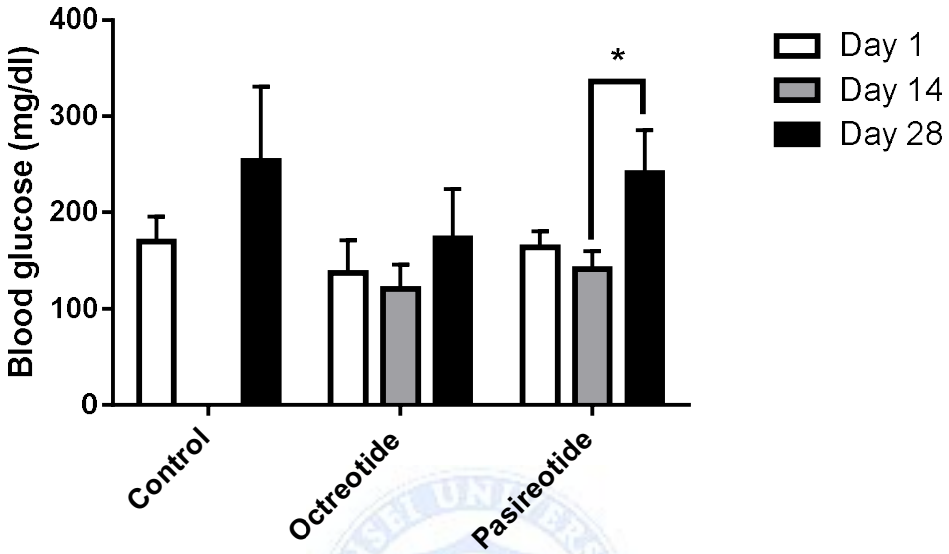

Figure 3. The changes inblood glucose levels. Pasireotide LAR (320mg/kg) and octreotide LAR (320mg/kg) were injected subcutaneously once a month to the mice for each group. Blood glucose levels were measured using a glucometer. Data are expressed as mean±SD (n=4). *P<0.05.

IV. DISCUSSION

This is the first study to show the biochemical effects of somatostatin analogs, especially pasireotide, on the mice which have the deletion of aryl hydrocarbon receptor interacting proteininsomatotroph (sAIPKO) and the results were similar tothose of previous studies based on human subjects.[2,22]With my results, the mouse model could be useful indeveloping therapeutics for GH-secreting pituitary tumor in the near future.

Mice in which Cre-recombinase is expressed in pituitary somatotrophs were developed by Luque et al.[29] In these mice, 310 bp 5` of the initiation codon of the rat GH gene (*rGHp*) is used to target pituitary somatotrophs, and the resulting transgene, when expressed, permits selective Cre-mediated recombination of loxP-modified alleles in somatotroph-derived cells of the anterior pituitary. *rGHp-Cre*$^{tg/+}$; *AIP*$^{lox/+}$ mice were obtained by crossing rGHp-Cre$^{tg/+}$ female mice with male AIP $^{lox/lox}$ mice. Interbreeding of *rGHp-Cre*$^{tg/+}$; *AIP*$^{lox/+}$ mice produced homozygous disruption of the AIP gene in somatotrophs(*rGHp-Cre*$^{tg/+}$; *AIP*$^{lox/lox}$).

rGHp-Cre$^{tg/+}$; *AIP*$^{lox/lox}$(sAIPKO) mice exhibit normal embryonic and postnatal development, and display an unaltered distribution of anterior pituitary cell types. At 48 weeks old age, sAIPKO mice had significantly larger body weight than *AIP*$^{lox/lox}$littermate mice (control). Overall, 40% of sAIPKO mice developed pituitary adenomas by 24 weeks of age and more than 80% developed pituitary adenomas by 40 weeks. The incidences of pituitary tumor were similar among males and females.

sAIPKO mice had no morphologic abnormality in other neuroendocrine organs. On histological examination, pituitary adenomas of sAIPKO mice appeared highly invasive.

Acromegaly is a chronic neuroendocrine disorder caused by excessive levels of growth hormone (GH) that drive the overproduction of insulin-like growth factor 1 (IGF-1). In over 90% of cases, the origin of GH hypersecretion is a benign pituitary somatotroph adenoma.[23] Clinical manifestations of the disease range from subtle acral enlargement to more serious consequences, such as diabetes mellitus, hypertension, and respiratory and cardiac failure.[24]Furthermore, the rate of mortality in the patients with acromegaly who have elevated GH and IGF-1is greater than in the general population.[4]However, normalizing GH and IGF-1 levels restores the standardized mortality ratio in patients with acromegaly.[3] Thus, the principal goals of treatment for acromegaly are to lower GH and normalize IGF-1 levels, and to prevent further tumor growth or even induce tumor shrinkage.[25]

Although the transsphenoidaladenomectomy is the treatment of choice, some patients do not achieve the biochemical remission after surgery and requiremedical treatment. However, there are not many available drugs due to the limitations of GH secreting pituitary adenoma which include the poorly understood pathogenesis and lack of proper animal models. I recently developed the mouse model which has the deletion of aryl hydrocarbon receptor interacting protein in somatotroph(sAIPKO) using rGHp-Cre^{tg} mice. According to my previous data, almost 80% of the mice developed pituitary adenomas without morphologic abnormality in other

neuroendocrine organs.In addition, the tumor appeared highly invasive on histological examination.

Pasireotide is distinguished from other somatostatin analogs by its binding profile. It has a broader binding spectrum, with high-affinity binding to receptors somatostatin receptor (SSTR) 2,3, and 5 and moderate affinity for SSTR1. The broadened selectivity of pasireotide, especially with regard to SSTR5, supports its clinical utility for somatotroph and corticotroph pituitary tumors along with other neuroendocrine tumors that express multiple SSTRs.[26] Recently, Colao and collegues showed that pasireotide LAR demonstrated superior efficacy over octreotide LAR and is a viable new treatment option for acromegaly.[2]Gdelha and collegues also demonstrated that pasireotide provides superior efficacy compared with continued treatment with octreotide or lanreotide in patients with acromegaly who are inadequately controlled using first-generation somatostatin analogs.[22]My study showed that Pasireotide has stronger inhibitory effect on excessive IGF-1 levels on sAIPKO mice than octreotide similar to previous clinical studies suggesting that the mouse model represents more aggressive GH secreting adenoma and might be useful to develop therapeutics for acromegaly in the near future.

Somatostatin is an inhibitor of both insulin and glucagon secretion by binding to SSTR2 and SSTR5 which are the predominantly expressed subtypes in human pancreatic islet cells.[27] The predominant expression of SSTR5 on cells and SSTR2 on α cells was found in human islet cells.[28]Schmid and collegues suggested that hyperglycemia caused by pasitreotidecould be explain by the expression pattern of

SSTRs in rat pancreatic islet cells and demonstrated that this effects was transient with tachyphylaxis on rats.[12] However, in my study, mice in the pasireotide-treated group developed hyperglycemia on the 28th day, not on the 14th day. This different result might be explained by metabolic differences or the difference of SSTR expression on pancreatic islet cells in sAIPKO mice which probably have GH secreting pituitary tumor, comparing with normal population. Recently, in clinical studies for pasireotide in patients with acromegaly, hyperglycemia and diabetes mellitus were more frequently reported in the groups on pasireotide.[2,22]

This study demonstrated that pasireotide LAR achieved greater suppression of IGF-1 than octreotide LAR on somatotroph specific AIPKO mice, while pasireotide LAR caused hyperglycemia more frequently than octreotide LAR on the mice similar to the previous studies for the drugs on patients with acromegaly suggesting that the mouse model could be a standard mouse model for aggressive GH secreting pituitary adenoma and be useful indevelopingnew therapeutics for the disease.

V. CONCLUSION

Pasireotide, which is a multireceptor targeted somatostatin analog, had a superiority over octreotide to control biochemical activity of GH secreting pituitary adenoma in sAIPKO mice, suggesting that this mouse model representsthe aggressive type of the disease. Thus, this mouse model is promising to be useful in developing new drugs and evaluate the efficacy of them for GH secreting pituitary adenoma.

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ABSTRACT (IN KOREAN)

뇌하수체 선종 연구에 있어서 sAIPKO 마우스 모델의 유용성

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이우경

말단 비대증은 주로 성장호르몬 분비 뇌하수체 종양에 의해서 성장호르몬이 과다 분비되어 생긴다.일차적 치료는 경접형골 수술이지만 어떤 환자들은 수술 후에도 성장호르몬 조절에 실패하여 약물치료를 필요로 한다.하지만,이러한 병은 드물고,이를 대표할 수 있는 모델이 없어 병리기전이 잘 밝혀져 있지 않기 때문에 치료제 개발 연구에 많은 제한이 있고 따라서 사용할 수 있는 약이 많지 않다.최근 우리는 성장자극세포에 특이적으로 AIP (aryl hydrocarbon receptor interacting protein)유전자를 삭제하여 성장호르몬 분비 뇌하수체 종양을 유발하는 쥐 모델 (sAIPKO)을 개발하였다.이러한 쥐 모델이 성장호르몬 분비 뇌하수체 종양 치료제 개발에 유용한 모델이 될 수

있는지 확인하고자 이 쥐들에 현재 말단비대증 치료제로 알려져 있는 소마토스타틴유사체들 (octreotide, pasireotide)을 투여한 뒤 그것들의 효과를 평가하였다.Octreotide를 투여한 군에서는 Insulin like growth factor 1(IGF-1)가 줄어들지만 통계학적으로 유의하지 않는 반면,Pasireotide를 투여한 군에서는 IGF-1이 통계학적으로 유의하게 줄어들었다.그리고 Octreotide를 투여한 군에서 혈중 혈당 수치의 변화는 없었던 반면,Pasireotide를 투여한 군에서는 혈중 혈당 수치가 4주뒤 유의있게 증가된 것을 알 수 있었다.여러 소마토스타틴 수용체에 강하게 작용하는 pasireotide는 sAIPKO쥐 모델에서 생화학적 조절에 있어서 octreotide에 비해 두드러진 효과를 보였다. 이는 sAIPKO mouse가 좀 더 공격적인 성장호르몬 분비 종양을 반영할 수 있다는 것을 시사하고,따라서이 쥐 모델은 향후 성장호르몬 분비 뇌하수체 종양의 치료제 개발에 있어서 유용할 것이다.

핵심되는 말 :말단비대증,아릴 하이드로카본 수용체 작용 단백질,소마토스타틴 유사체