

## News Release

### Title

Hypothalamic Contribution to Pituitary Functions is Recapitulated in vitro Using 3D-cultured Human iPS Cells

### Key Points

- Successful differentiation from human iPS cells to pituitary hormone-producing cells.
- By creating the hypothalamic-pituitary unit, it became a functional tissue that responds to the surrounding environment, such as hypoglycemia.
- Expected to be a fundamental technology for future regenerative medicine as well as a method to clarify the relationship between the pituitary and hypothalamus.

### Summary 1

Graduate student Takatoshi Kasai (1st author), Associate Professor Hidetaka Suga (corresponding author), Professor Hiroshi Arima and their collaborators in the Department of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu), established a differentiation method for mature and functional pituitary hormone-secreting cells using human induced pluripotent stem cells (human iPS cells).

The pituitary gland is an endocrine organ which secretes hormones according to the surrounding environment and plays an important role in maintaining systemic homeostasis. When the pituitary gland becomes dysfunctional, various symptoms appear due to the lack of hormones and in particular, adrenocorticotrophic hormone (ACTH) deficiency may cause a life threat.

In 2016, this research group succeeded in inducing the pituitary hormone-secreting cells from human embryonic stem cells (human ES cells). By improving the differentiation method with human iPS cells, they made a success in the simultaneous induction of hypothalamic progenitor cells during the process of pituitary hormone-secreting cell differentiation. After long-term culture for 150-200 days staying the two tissues adjacent, they succeeded in creating an aggregate in which pituitary hormone-secreting cells and hypothalamic hormone-secreting cells coexist (hypothalamic-pituitary unit). This hypothalamic-pituitary unit had an improved ability to secrete hormones, equivalent to that of adult mouse pituitary cells. When the hypothalamic-pituitary unit was exposed to low glucose, the secretion of ACTH increased. These data suggest that the hypothalamus and the pituitary gland collaborate to respond to low glucose. It is possible to consider that the hypothalamic-pituitary unit is a functional organoid that reacts to the surrounding environment.

This method is expected to contribute to regenerative medicine, elucidation of the relationship between the pituitary and hypothalamus, and pathological examination of

pituitary disease.

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## **Summary 2**

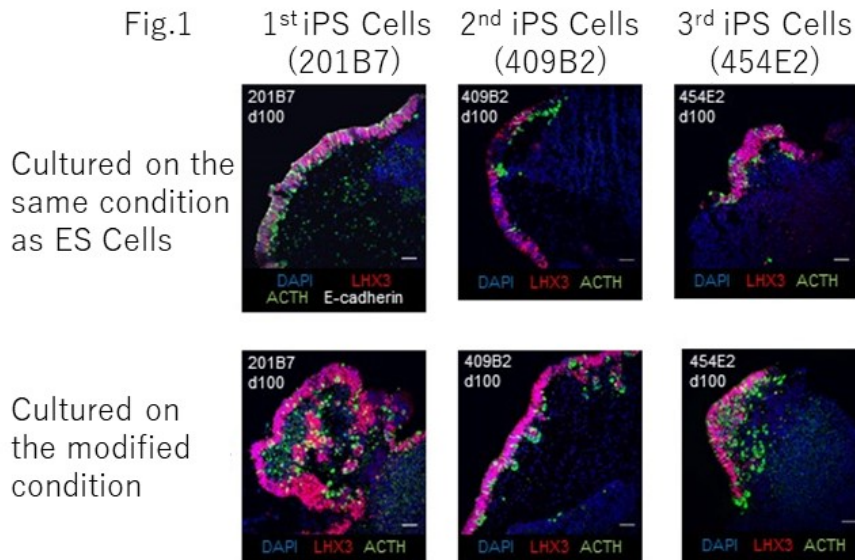
Kasai and Suga *et al.* have established the differentiation method of functional hypothalamic-pituitary units using human iPS cells. ACTH secretion capacity from induced pituitary cells increased to the same level as adult mice anterior pituitary cells. Hypothalamic-pituitary unit responded to environmental stimulation such as low glucose through the CRH-ACTH pathway.

## **Research Background**

The pituitary gland plays a critical role in controlling systemic hormones and a wide variety of life phenomena such as growth, metabolism, and stress response. Therefore, when the function of pituitary hormone-producing cells declines, various symptoms appear. The lack of adrenocorticotrophic hormone (ACTH) can cause adrenal insufficiency and can be life-threatening. Hormone replacement is the current therapy against hypopituitarism. However, there remains a problem that the current hormone administration cannot sufficiently cope with the fluctuating hormone requirements. It is difficult to avoid both the risk of adrenal insufficiency due to hormone deficiency and the risk of diabetes and hypertension by excessive hormones. If we can create hormone-producing cells that can respond to the surrounding environment, it may become a better treatment than the replacement therapy. In 2016, this research group succeeded in inducing the differentiation of pituitary hormone-secreting cells from human embryonic stem cells (human ES cells). In this report, they tried to use human induced pluripotent stem cells (human iPS cells) for producing the functional pituitary cells.

## **Research Results**

They succeeded in inducing ACTH-positive cells by culturing three types of human iPS cells under the same conditions as those for human ES cells. When the number of cells at the start of culture and the concentration of reagents were changed to increase the differentiation induction efficiency, the induction efficiency tended to increase (Fig.1).



Hypothalamic progenitor cells were also induced simultaneously during the differentiation induction process. As a result of long-term culturing for about 150-200 days in the state where these are adjacent to each other, a tissue in which pituitary hormone-secreting cells and hypothalamic hormone-secreting cells coexist in one aggregate (hypothalamic-pituitary unit). ACTH positive cells were found in the pituitary region, and hypothalamic hormone positive cells such as adrenocorticotrophic hormone releasing hormone (CRH) were found in the hypothalamus region (Fig.2). By culturing the hypothalamic-pituitary unit for a longer time, ACTH increased until day 300 (Fig. 3).

Fig.2

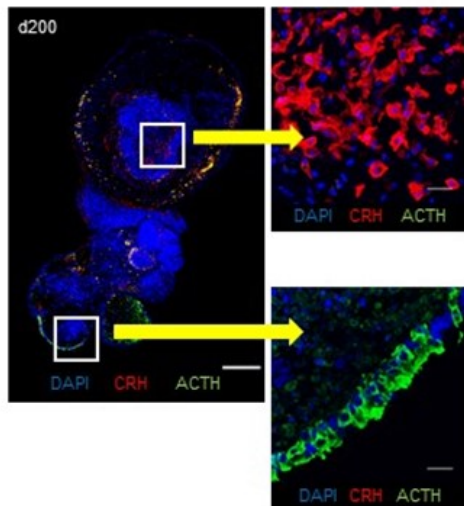
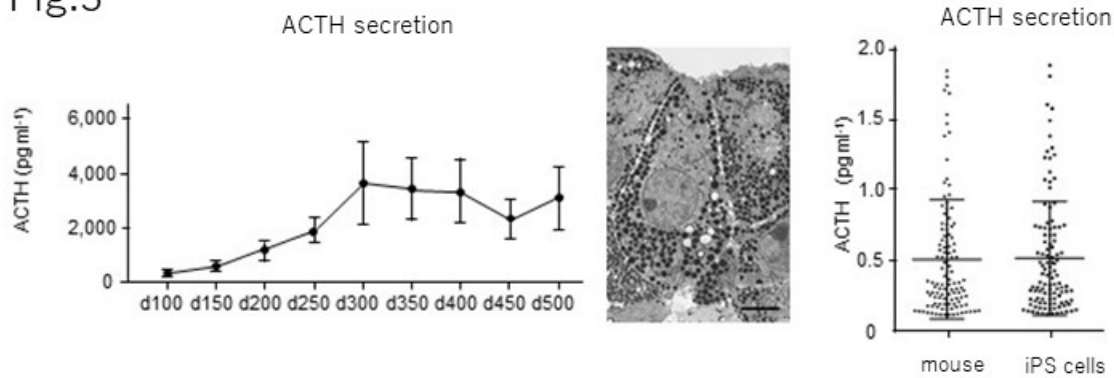
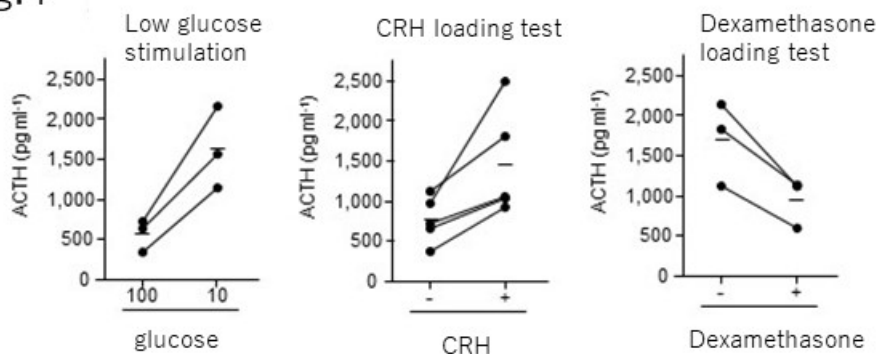


Fig.3



When the hypothalamic-pituitary unit was exposed to low glucose, the secretion of ACTH increased. In vivo, the pituitary gland works under the control of the hypothalamic CRH, and this result suggests that the hypothalamus and the pituitary gland work in association with low glucose. ACTH increased with CRH loading, and ACTH decreased with dexamethasone loading. The hypothalamic-pituitary unit was considered a functional organoid that responds to the surrounding environment (Fig. 4).

Fig.4



### Research Summary and Future Perspective

In this study, they created a functional pituitary gland from human iPS cells, which is applicable to regenerative medicine. Since the tissue with both pituitary and hypothalamus could be induced, it can be expected as a model for elucidating the relation between pituitary and hypothalamus. It is also thought to be useful for pathogenesis of pituitary diseases.

### Publication

Takatoshi Kasai<sup>1</sup>, Hidetaka Suga<sup>1</sup>, Mayu Sakakibara<sup>1</sup>, Chikafumi Ozone<sup>1</sup>, Ryusaku Matsumoto<sup>2</sup>, Mayuko Kano<sup>1</sup>, Kazuki Mitsumoto<sup>1</sup>, Koichiro Ogawa<sup>1</sup>, Yu Kodani<sup>3</sup>, Hiroshi Nagasaki<sup>3</sup>, Naoko Inoshita<sup>4</sup>, Mariko Sugiyama<sup>1</sup>, Takeshi Onoue<sup>1</sup>, Taku Tsunekawa<sup>1</sup>, Yoshihiro Ito<sup>1</sup>, Hiroshi Takagi<sup>1</sup>, Daisuke Hagiwara<sup>1</sup>, Shintaro Iwama<sup>1</sup>, Motomitsu Goto<sup>1</sup>, Ryoichi Banno<sup>1</sup>,

Jun Takahashi<sup>5</sup> & Hiroshi Arima<sup>1</sup>

<sup>1</sup>Department of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan.

<sup>2</sup>Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe 650-0017, Japan.

<sup>3</sup>Department of Physiology, Fujita Health University, Toyoake 470-1192, Japan.

<sup>4</sup>Department of Diagnostic Pathology, Toranomon Hospital, Tokyo 105-8470, Japan

<sup>5</sup>Department of Clinical Application, Center for iPS Cell Research and Application, Kyoto University, Kyoto 606-8507, Japan

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