CRH is a stimulator for both connective tissue- and mucosal-type mast cells.

Mika Takaichi[1], Koji Sugawara[1], Yukari Mizukami[1], Ralf Paus[2] and Daisuke Tsuruta[1]

[1] Department of Dermatology, Osaka City University Graduate School of Medicine, Osaka, Japan
[2] Department of Dermatology & Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, USA

Background

It is well-known that psychological stress exacerbates various types of diseases including atopic dermatitis and allergic rhinitis (1,2). Mast cells (MC)s are essential cells in immune response and play pivotal roles in allergic disease. Both the increased number of MCs and their degranulation are observed in various types of skin diseases, including atopic dermatitis and allergy. Hypothalamic pituitary adrenal (HPA) axis is an essential endocrine system of reaction to stress in our body including skin. Corticotropin-releasing hormone (CRH) is regarded as a potent central stress mediator. We have previously shown that the locally secreted CRH activates connective tissue type MCs (CT-MC)s degranulation and differentiation by organ cultured human hair follicles (HF)s (3). Here, we focused on the effect of CRH on mucosal-type (M-)MCs biology compared to CT-MCs.

Methods, Results, Discussions

Using the previously established human nasal polyp organ culture (Fig.1) (4), CRH immunohistochemistry shows the positive CRH immunoreactivity within the epithelium and some cells within the lamina propria of freshly isolated human nasal polyps (Fig.2). Next we checked whether the local HPA axis exists in nasal mucosa. We performed RT-PCR using nasal polyps. As a result, not only CRH but also CRH receptor (CRHR) type1 and type2, ACTH, ACTH receptor (MC2R), Glucocorticoids receptor (GR, NR3C1) are detected in gene levels within human nasal polyps (Fig.3). In addition, we found that CRH (10^{-7} M) treatment increased immunoreactivity of both MC2R and GR of organ-cultured human nasal polyps (Fig.4). These results suggest that human mucosa may have local HPA axis. Furthermore, hydrocortisone treated nasal polyp showed decreased CRHR expression (Fig.5). This suggests the existence of positive and negative feedback system as seen in central nerve system. We next checked the effect of CRH on M-MCs and found that degranulated M-MCs number increased in CRH treated organ-cultured human nasal polyp (Fig.6).

In addition, CRH increased total tryptase+ M-MCs number as well as Ki-67/tryptase double-positive M-MCs number (Fig.7,8). This indicates that CRH stimulated M-MCs proliferation *in situ.*

Just seen in human HFs, CRH increased the expression of stem cell factor (SCF), a growth factor for MCs, suggesting that SCF is also involved in CRH-induced M-MCs activation (Fig.9). Furthermore, the increased number of MCs by CRH was abrogated by the co-administration of anti-SCF or CRHR type1 specific antagonist, antalarmin (Fig.10). We next investigated how CRH affects the expression of CRHR on M-MCs by CRHR/tryptase double immunohistochemistry. This showed that CRH increased the number of CRHR positive M-MCs *in situ* (Fig. 11). This suggests that CRH by itself increased the susceptibility of M-MCs to CRHR.

These results indicate that stress may activate M-MCs. To confirm this, we evaluated M-MCs in nasal mucosa of chronic restraint stress model mice. As a result, both the number of degranulated and total M-MCs seemed to significantly increased in nasal mucosa (Fig.12).

Conclusion

Current results suggest that the local HPA axis exists not only in human skin but also in nasal mucosa. Since CRH is a stimulator for both CT-MCs and M-MCs, controlling of HPA axis-related hormones may be a key target for establishing novel therapy for atopic dermatitis and allergic rhinitis.

Fig.1

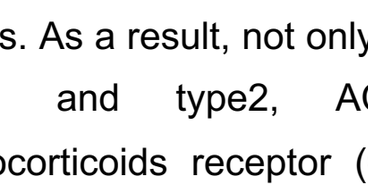
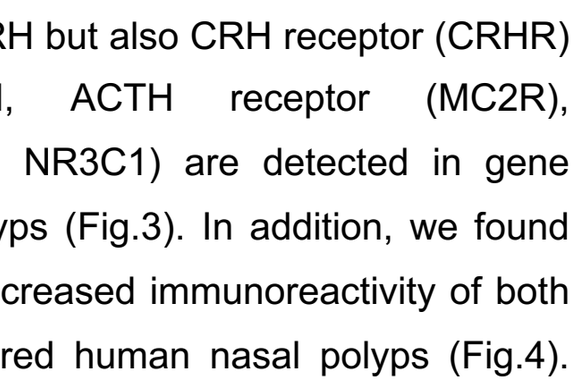


Fig.2



Red : CRH positive cell

Fig.3

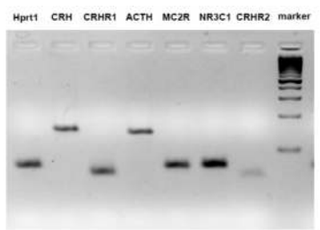
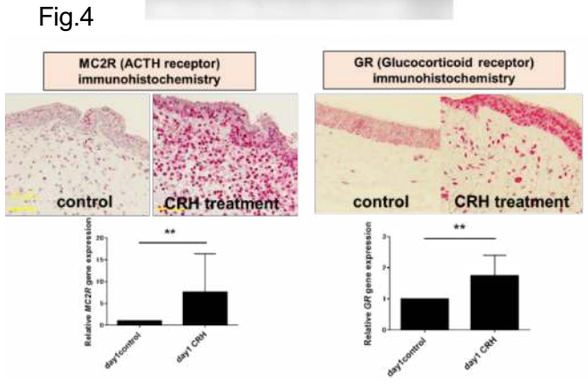


Fig.4



＊ p<0.05、＊＊ P<0.01、 ＊＊＊P<0.005

Fig.5

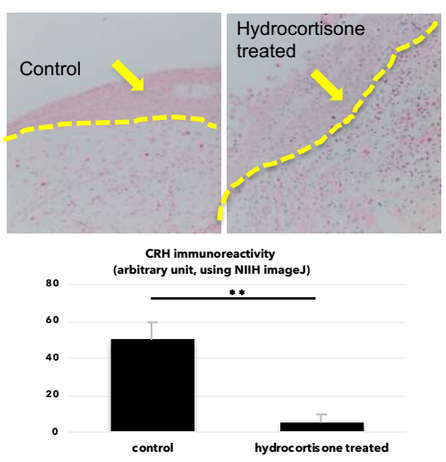


Fig.6

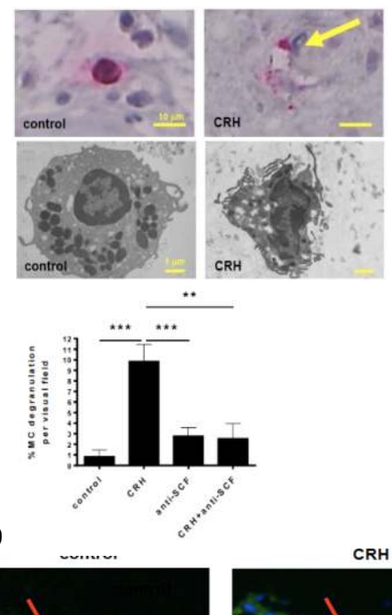


Fig.7

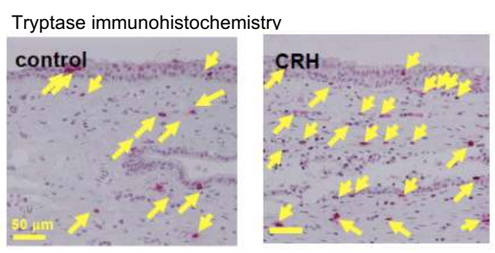


Fig.8

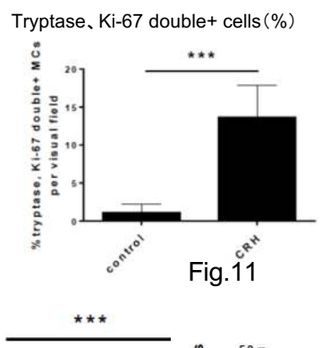


Fig.9

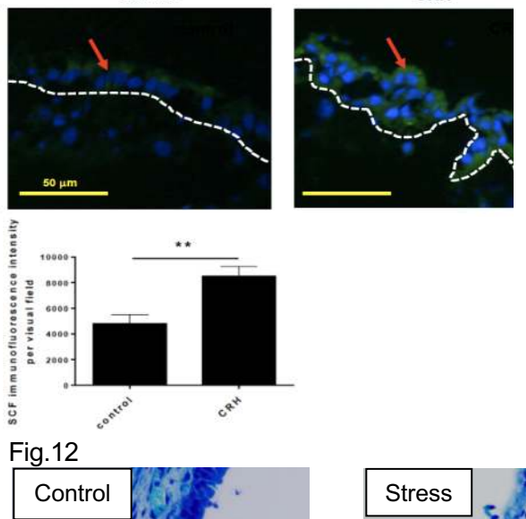


Fig.10

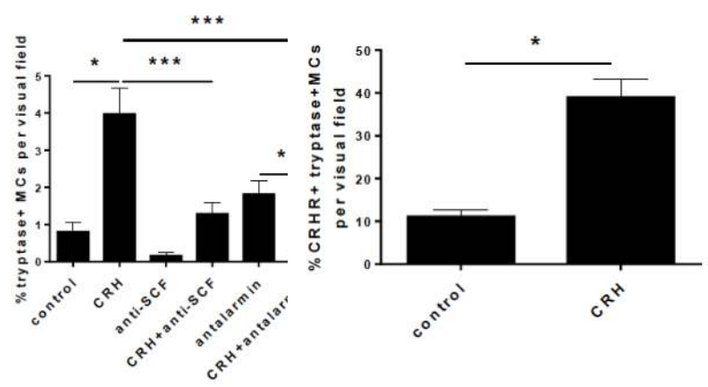
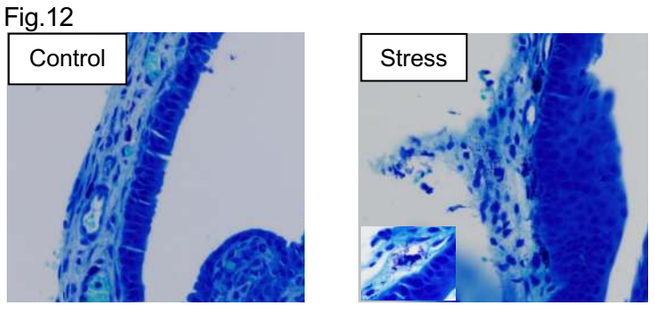
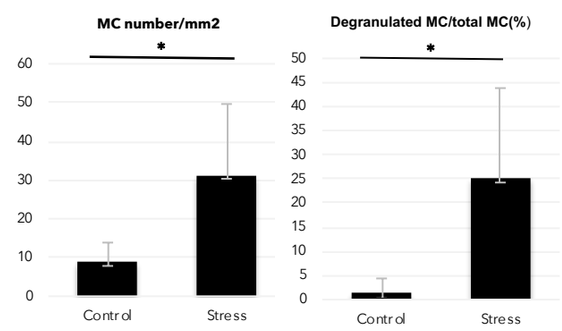


Fig.11

Fig.12





[Refference]

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2) Miyasaka T et al. *Allergol Int*. 2018
3) Ito N et al. *J Invest Dermatol.* 2010
4) Sugawara K et al., J Allergy Clin Immunol 2013