Does PACAP have the potential to be a revolutionary role for the prevention of dry eye?

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Description

Since the discovery of adrenaline at the beginning of the 20th century in 1900, a number of bioactive substances have been identified that are involved in maintaining homeostasis in the organism. However, many bioactive substances, especially peptides, are low in toxicity, and it is easy to reach target organs and organs with small molecules, but their blood half-life is very short and they have shortcomings to be metabolized immediately *in vivo*, making clinical applications difficult. However, there are many peptide drugs that are actually helpful in the clinic, such as anticancer drugs (LHRH), antihypertensive drugs (hANP), and antidiabetic drugs (GLP-1), and peptide drug discovery has already been documented to be helpful.

PACAP is a neuropeptide isolated and purified by Miyata, et al. [1] based on increased cAMP activity in anterior pituitary cells. PACAP was first identified as the agent that activates adenylyl cyclase and enhances the production of cAMP among various active substances in the brain. It has also been shown that the affinity for PACAP receptors differs by as much as 1000-fold, even though the amino acid composition is 70% the same as VIP, which are similar members of peptides including glucagon, secretin family [1]. The cAMP elevation by PACAP is extremely potent compared to other neuropeptides and is the most potent cAMP elevator *in vivo*. PACAP and its receptors are expressed in the central and peripheral nervous system and in peripheral organs (e.g., testis, adrenal gland, and intestinal tract). It has been reported that the control of hematopoietic stem cells is carried out by the sympathetic nervous system and that the proliferation of neural stem cells is reduced in immunocompromised animals. We showed that sympathetic nerves enter the bone marrow and that the surrounding Schwann cells regulate the function of hematopoietic stem cells *via* TGF-β (Transforming Growth Factor-β), which is one of the key cytokines that maintains the homeostasis of the organism, and its aberration is a key factor involved in the progression and life support of various diseases [2]. PACAP may regulate the immune system in a neuronal and humoral manner in the bone marrow [3]. Numerous reports have focused on the applicant and others on the central effects of PACAP, and it has been demonstrated in the hippocampal injury model animals that PACAP has not only neuroprotective effects but also neurogenic and regenerative effects after brain ischemia [4].

We incidentally discovered that dry eye-like manifestations are seen in the corneal epithelium of the eye during the course of a study in PACAP KO mice [5,6]. The animals showed markedly reduced tear secretion and manifestations such as thickening of the corneal epithelium and neovascularization. Why does the absence of PACAP expression lead to decreased tear secretion and dry eye symptoms? We conducted an animal study to answer this question, which revealed for the first time that PACAP activates an aquaporin molecule (AQP5) that is critical for water secretion within acinar cells of the lacrimal gland and promotes tear secretion [5]. PACAP was found to stimulate acinar epithelial cells of the lacrimal gland to enhance intracellular cAMP production and activate AQP5 to secrete intracellular water molecules into the exterior. One instillation of PACAP was also found to increase tear discharge for as long as 2 hours. More recently, we found that PACAP is also directly involved in the regeneration of epithelial and endothelial cells of the cornea in culture studies Nakamachi, et al. [5]. However, the entity of the regenerative and neoplastic effects of corneal epithelial cells induced by PACAP is unknown, and the intracellular molecular mechanisms are completely unknown.

Why is it necessary to study dry eye? And what is the specific countermeasure? Dry eye is a corneal injury caused by a decrease in tear volume or a change in tear composition. Currently there are 22 million patients in Japan and as many as 340 million patients with dry eye worldwide. If dry eye worsens, there is a risk of not only corneal damage but also blindness. Current treatments for dry eye are mostly symptomatic, with some drugs for dry eye (e.g., Diaquas, Hyalein), but their effects are very short-lived and therefore no causative treatment is available. It is also known that the regenerative capacity of the corneal epithelium decreases markedly with aging in many patients with dry eye. In that sense, if PACAP is used as a seed for drug discovery, the above issues can be solved.

However, since the half-life of this peptide is as short as 15 minutes, it is necessary to discover new small-molecule compounds by exploration and synthesis. It is considered that the rapid increase in the number of dry eye patients can be suppressed if this research is carried out, and that it is useful for the health maintenance of many nationals both at home and abroad, and that the social contribution is also very big. In addition, if the synthesis of small molecule agonist is possible, it can be applied for prevention and treatment of the dry eye, and in addition, it may be used as a corneal protective agent for repairing medicine after cataract and LASIK operation and for preventing and treating glaucoma, and the application range is very wide. In addition, it may be applied in the future for the treatment of patients with Sjögren's syndrome, a dry syndrome, and glaucoma. We are convinced that the performance of this study will bring wellbeing to many people, including those with dry eye and other dry syndromes. It is expected that PACAP will be an efficacious treatment for dry eye in the

future, and it is recommended that PACAP and its analogues be used as preventive and ameliorative drugs for dry eye.

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