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Study on Skin and Eccrine Sweat Glands

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INTRODUCTION

Dr. Y. Kuno's pioneering work in the field of human sweating is considered by many physiologists excellent. However, two important problems remain to be elucidated. First, is the central mechanism of sweating and second, is the relationship between peripheral mechanisms and the innervation of sweat glands as well as the role of neurotransmitters. This paper will discuss current trends and our research work in the field of human sweating study.

Novel approach to the analysis of human sweating

The development of a severe combined immunodeficient mice (BALB/cA-nu, scid) which is a hybrid between BALB/cA-nu and CB-17-scid mouse made it possible to transplant and study the human skin. This heterologous human skin graft provides a novel model in the study and detailed analysis of human eccrine sweat glands. This system further provides and in vivo model to understand the mechanisms of human sweating.

The BALB/cA-nu, scid mouse was first developed at the Kanagawa Academy of Science and Technology and the School of Medicine, Tokai University. Since 1985 our department has collaborated with the Central Institute of Experimental Animals and has used the BALB/cA-nu, scid mouse in our study.

Interesting Problems in the field of human sweating studies.

Inspite of the numerous research work done by T. Ogawa (Aichi Medical School) and M. Kosaka (Inst. of tropical Medicine, Nagasaki) as well as the numerous publications on vasoactive intestinal polypeptide (VIP) which was identified as a transmitter of sudomotor nerve endings, there are still several unanswered questions remaining:

1. sudomotor nerve-sympathetic nerve (cholinergic-partially adrenergic) dual innervation.
2. analysis of mental, gustatory and thermal sweating.
3. peripheral mechanism of secretion of the neurotransmitter from the sympathetic nerve endings.
4. sensitivity of the sweat gland cells (eccrine and apocrine sweat glands of humans and animals).

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5. analysis of the relationship between the central nerve impulses and peripheral nerve impulses on sudorific mechanisms.
6. applications of molecular biology techniques in the analysis and correlation between hyperthermia-fever and sweating.

It is extremely important to elucidate these problems for the proper understanding of human sweating.

Progress of Sweat Study

Table 1 shows some information on sudorific findings in humans and animals.
Table 2 lists some of the important unanswered problems on eccrine sweating.

Table 1. Up to date research results on sweat secretion
−Is it really correct findings?−

Subject	Sweat category	Sweat gland	Neurotransmission
Human	mental sweating	Eccrine	Cholinergic-Adrenergic
	gustatory sweating	Eccrine	do.
	thermal/mental	Apocrine/Eccrine	do.
	thermal sweating	Eccrine	do.
Animal	mental sweating	Eccrine	Cholinergic-Adrenergic
(Horse)	thermal sweating	Apocrine	Adrenergic
(Other animals)	thermal sweating	Apocrine	Adrenergic

(Kosaka M. *et al,* 1994)

Table 2. Expected new findings on mechanism of sweating

Subject	transplanted skin into BALB/cA nu. mouse	Problems to be solved
Human	palmar & plantar	How about
	facial	(1) sweat category?
	axillar	(2) Sweat gland?
	general body surface	(3) Neurotransmission?
Animal	Palmar & plantar	
(Horse)	general body surface	
(Other animals)	do.	

(Kosaka M. *et al,* 1994)

Fig. 1 shows the scheme of this study: Sweating was induced by topical application of neurotransmitters to the heterologous human skin transplanted onto the BALB/cA-nu, scid mouse. This process could be detected either by the Minor's method (iodine-starch reaction), Magnetic Resonance Imaging (MRI) or the macroscope.

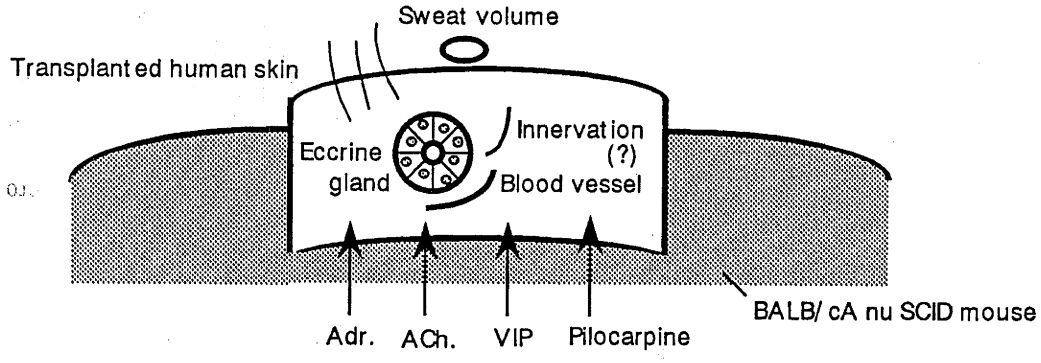

Fig. 1: Sweating of the human skin transplanted into the BALB/cA-nu SCID mouse

This new method as shown in Fig. 2 can shed light into the phenomenon of eccrine and apocrine sweating as well as mental, gustatory and thermal sweating. This new method can also help study the difference among species.

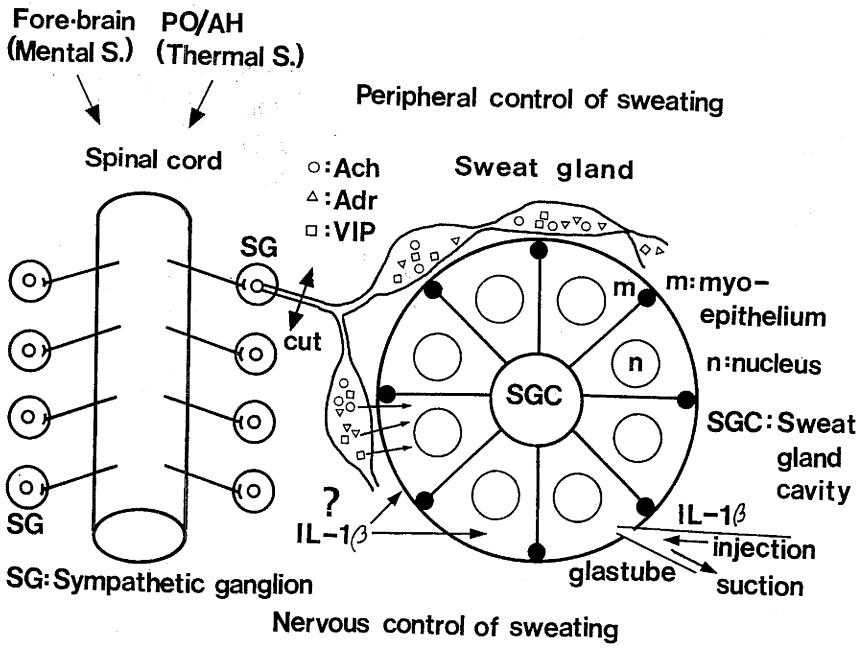

Fig. 2: Central and peripheral nervous control of sweating

In addition to the studies on sweat inducing or suppressing mechanisms of cathecolamine related substances such as Ach, pilocarpine, Adr, Nor-Adr, DOPA, dopamine, serotonin, atropine and mathacoline (MCH), attention has been focused on the evaluation and correlation between hyperthermia-fever-sweating system and IL-1 $\alpha\beta$, as well as heat shock proteins (HSPs). Studies are currently being done on other possible sweat inducing substances such as vasopressin (ADH), calcitonin gene-related peptide (CGRP), substance P, ANP, galamine, neuropeptide Y (NPY), VIP, LPS, neurotensin and bombesin. There are also some clinical reports examining the direct effect of exotoxins (e. g. tetanus, botulinus) on sweat glands. Aside from the in vitro studies on isolated eccrine glands, most of the investigations have not fully elucidated the mechanisms of sweating. There still questions that remain to be answered. It is expected that studies involving heterologous human skin transplanted into BALB/cA-nu, scid mouse can contribute to the elucidation of these remaining problems. Moreover, BALB/cA-nu, scid mice can be used in other disciplines such as immunology and carcinogenesis.

RECENT FINDINGS

Recently, there has been great interest in VIP, IL-1 $\alpha\beta$, HSPs as substances that can act directly on the sweat glands. While it is known that local heating induces the secretion of Ach from the sudomotor nerve endings, the responsiveness of the sweat gland itself to the neurotransmitters also increases. In 1980, VIP was found to exist in the cholinergic nerve endings of human exocrine glands and sudomotor nerve endings of the cat's foot pads. Sudomotor nerve impulse induces the secretion of Ach and VIP. It is supposed that the effect of VIP on sweat glands is the dilation of the circumferential vein. Accordingly, venous dilation is not obstructed even when sweating is suppressed by the application of atropin. A number of studies have been done on the effects of the central nervous system activities (from cortex to spinal level) on sweating. The analysis however becomes much more complicated if one correlates the sweat stimulating effects of biological hormones, amino acids and collateral nerve impulses. Current data as shown in Table 3 shows clear evidence of

Table 3. Effect of chemical stimulation on human sweat gland in the nude SCID mouse

Chemical Stimulant / Animal	Adrenaline			Pilocarpine			Atropine + Pilocarpine			VIP
	(re)	(spots)	(area)	(re)	(spots)	(area)	(re)	(spots)	(area)	
CB-17 SCID	+	4	0.109	+	5	0.103	−			nt
BALB/cA nu. SCID (N=4)	+	8	0.284	+	14	1.830	+	8	0.314	nt
	+	3	0.038	−			−			−
	−			+	4	0.077	−			−
	−			+	13	0.098	−			−

(re): response, whether sweat were induced (+) or not (−).
(spots): the number of sweat spots.
(area): area wetted by swaet (mm^2).
nt: no trial
(Shimazu M, Kosaka M, et al, 1994) unpublished data

adrenergic sweating. The sweat stimulating effect of VIP is probably an indirect action to the sweat glands as suggested by previous studies. This novel approach will meet the expectation of clarifying unanswered question on human sweating.

Future Prospect

Visual techniques such as MRI will be necessary in the investigation and analysis of eccrine sweat glands.

In addition, more research on the neogenesis of the human skin (including eccrine sweat glands) is needed. This involves the mixture of human keratinocyte, fibroblast, stem cells of bone marrow and stem cells of the sweat gland being injected into the BALB/cA-nu, scid mouse subcutaneously. After injection, the injected cells form cysts followed by differential growth. In theory, neogenic human skin tissue is being organized inside the cyst. If this technique becomes successful it will now be possible to investigate the function of eccrine sweat gland using in vivo artificially formed human skin.

In conclusion, novel approaches to the investigation of human sweat glands allows us not only to obtain basic information but also enables us to explore new possibilities and hence come up with new findings on human sweating.

References

1) Cutler D. (1992): Cell biology. Progress by poisoning [news; comment]. Nature, 359, 773.
2) Hokfelt T., Johansson O., Ljungdahl A., Lundberg J. M. & Schultzberg M. (1980): Peptidergic neurones. Nature, 284, 515−521.
3) Kosaka M., Lee J. M., Matsumoto T. Tsuchiya K. & Ohwatari N. (1993): The role of heat shock proteins (HSPs) and interleukin-1 interaction in lowering of fever. p. 99 (348. 7/0), In XXXII Congress of the International Union of Physiological Sciences (ABSTRACTS), Glasgow
4) Kosaka M., Lee J. M., Yang G. J., Matsumoto T., Tsuchiya K., Ohwatari N. & Shimazu M. (1994): The role of heat shock proteins (HSPs) and interleukin-1 interaction in suppression of fever. pp. 35−39, In Temperature regulation; Advance in Pharmacological Sciences.
5) Kosaka M., Tsuchiya K., Ohwatari N., Matsumoto T. & Shimazu M. (1994): Sweat glands- Innervation of sweat gland-. SEITAI NO KAGAKU (in Japanese), 45 (4), 371−380.
6) Kuno Y. (1956): Human perspitation. pp. 1−416. Robert F. P. (ed.), Thomas CC, Springfield, Illinois, USA
7) Lundberg J. M., Anggard A., Fahrenkrug J., Hokfelt T. & Mutt V. (1980): Vasoactive intestinal polypeptide in cholinergic neurons of exocrine glands: functional significance of coexisting transmitters for vasodilation and secretion. Proc. Soc. Natl. Acad. Sci. USA, 77, 1651−1655.
8) Mcintyre B. A., Bullard R. W., Banerjee M. & Elizondo R. (1968): Mechanism of enhancement of eccrine sweating by localized heating. J. Appl. Physiol., 25, 255−260.
9) Ogawa T. (1970): Local effect of skin temperature on threshold concentration of sudorific agents. J. Appl. Physiol., 28, 18−22.
10) Ogawa T. (1972): Local determinants of sweat gland activity. pp. 93−108. In Itoh S, Ogawa K. &

Yoshimura H. (ed.). Advances in Climatic Physiology, Igakushoin, Tokyo.

11) Reitamo S, Anttila H. S., Didierjeam L. & Savarat J. H. (1990): Immunohistochemical identification of interleukin I alpha and beta in human eccrine sweat-gland apparatus. Br. J. Dermatol., 122 (3), 315−323.

12) Shimazu M., Tatsumoto T., Kosaka M., Ohwatari N., Tsuchiya K., Ueyama Y., Urano K., Kataki Y. & Saito M. (1996): A new approach to analysis of human sweating. Experientia, 52, 131−135.