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The Human Eccrine Sweat Gland: A Possible Growth Hormone Target Organ?

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1. INTRODUCTION

Human body temperature is regulated by the hypothalamic thermoregulatory center, which receives integrated inputs from central as well as peripheral thermal sensors. Subsequently, signals are emitted through effector pathways to regulate heat production, vasodilation and sweating. These effectors are influenced by hormonal factors, such as thyroxine, adrenaline and noradrenaline. Sweating occurs in many diseases (thyrotoxicosis, acromegaly and tuberculosis), indicating that sweat secretion is induced by toxins as well as by hormones. A direct effect of these factors at the level of the eccrine sweat gland cannot be excluded.

1.1 Physiological importance of sweating

In the resting state, sweating plays a minor role in the regulation of body core temperature. However, during physical activity or during heat stress, sweating becomes important for the maintenance of thermal balance. Short-term acclimatisation to work in heat results in a markedly improved sweating capacity that in turn leads to a significantly improved working capacity. Eight healthy volunteers exercised for 10 consecutive days at 60% of maximal aerobic power (VO_2 max) until the point of exhaustion at an ambient temperature of 40 °C. In this study it was shown that exercise endurance increased on average from 45 to 80 min after 10 consecutive days of exercise in a hot environment. The rise in body temperature was dependent on the sweating capacity of the individual, which improved with increasing degree of acclimatisation to work in the heat. Indeed, a high core temperature was the critical factor for exhaustion during exercise in hot environment [1].

Patients with anhidrotic ectodermal dysplasia represent a clinical example of the importance of sweating, as these patients are characterized by the lack of ability to sweat leading to lethal hyperthermia during febrile illness [2]. Furthermore, there is a marked difference in the ability to sweat exists between sexes in adults as well as in children [3,4]. Androgen and oestrogen receptors have been identified in human eccrine sweat glands [5], suggesting that sex steroids may affect sweat gland function.

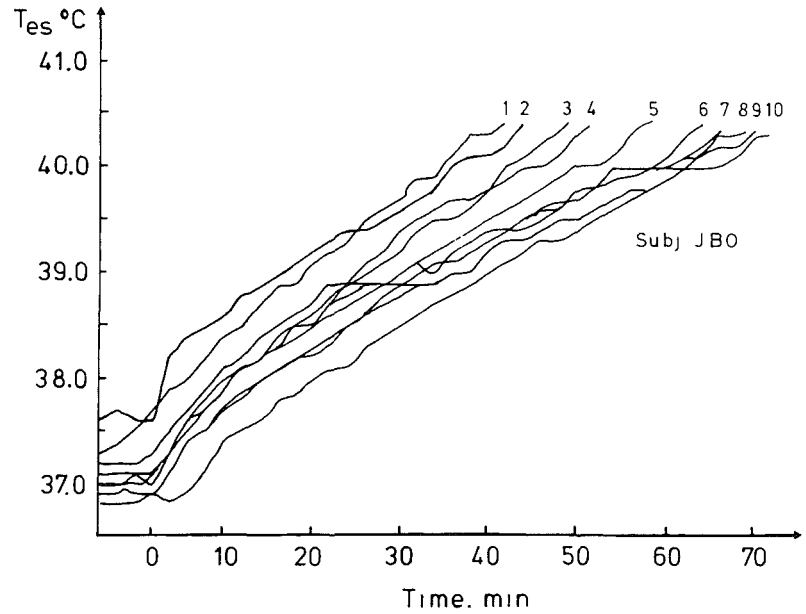

Figure 1. Oesophageal temperatures in one subject during ten consecutive days of exercise until exhaustion at 40 °Celsius. Sweating improved each day and was responsible for the markedly increased exercise endurance. Figure from ref [1].

2. GROWTH HORMONE SECRETION AND SWEATING

Sweating is often abnormal in patients with growth hormone (GH) secretory disorders. Thus, hyperhidrosis is a typical clinical feature of patients with acromegaly (excess GH because of a GH-producing pituitary tumour), although it has never been quantitated. Conversely, it has recently been shown that GH-deficient patients have a decreased sweating capacity as assessed by pilocarpine stimulation of the skin, and that sweating increases during GH treatment [4,6]. In addition, patients with the GH insensitivity syndrome have a reduced sweating capacity [7,8]. The pilocarpine iontophoresis test, which has been used (in a modified form) to demonstrate the decreased sweating in hypopituitary children and adults, was originally developed and utilized for the diagnosis of patients with cystic fibrosis [9]. However, this test has been shown to correlate with heat- and exercise-induced sweating, thus reflecting the physiological ability to sweat [10].

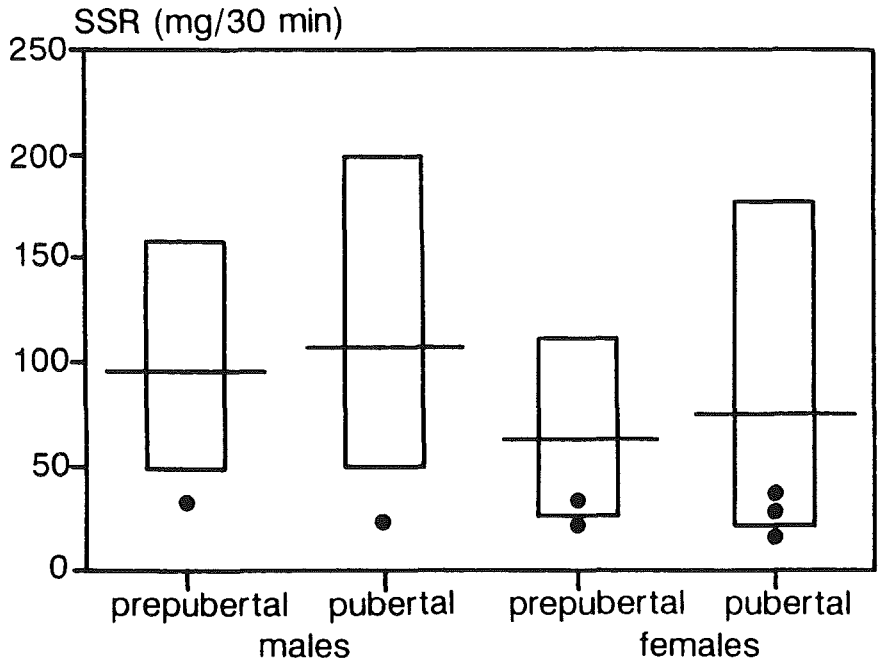

Figure 2. Sweat secretion rate (SSR) in 7 patients with GH insensitivity syndrome (●) as compared to healthy controls matched for sex and pubertal stage. The bars represent the 95% confidence intervals for healthy controls, and the vertical lines represent the geometric means. Figure from ref [8].

2.1 GH-deficiency and thermoregulation

Initially we reported on three cases of unexplained hyperthermia in GH-deficient adults off GH-treatment [11]. This prompted us to forward a hypothesis that GH-deficient patients are at risk of developing hyperthermia because of decreased sweating capacity. We demonstrated reduced sweating and consequently increased body heat storage in a pilot investigation of 6 GH-deficient patients who were not treated with GH [12]. During 30-min moderate exercise corresponding to 50% of the individual's VO_2 max, patients with GH-deficiency reached significantly higher body temperatures than age-matched controls [12]. Similarly, during a period of heat stress, the patients had decreased evaporative cooling and an increased body heat storage (accumulated body heat) as compared to controls [12]. Recently, these findings were confirmed in a large study of 16 GH-deficient adults who were treated with GH and therefore had normal Insulin-like Growth Factor I serum levels. These patients were studied during moderate exercise corresponding to 45% of VO_2max for 60 min at a room temperature of 35 °C. This study demonstrated significantly higher body core temperatures during exercise in patients as compared to controls [13].

Recent epidemiological data demonstrate that environmental temperature extremes clearly affect mortality from cardiovascular disease in healthy elderly people [14]. This is probably due to a decreasing ability to sweat with increasing age in addition to an impaired cutaneous vasodilation during heat stress [15]. Also secretion of GH declines with increasing age, but a causal link between these two age-related phenomena has not been demonstrated.

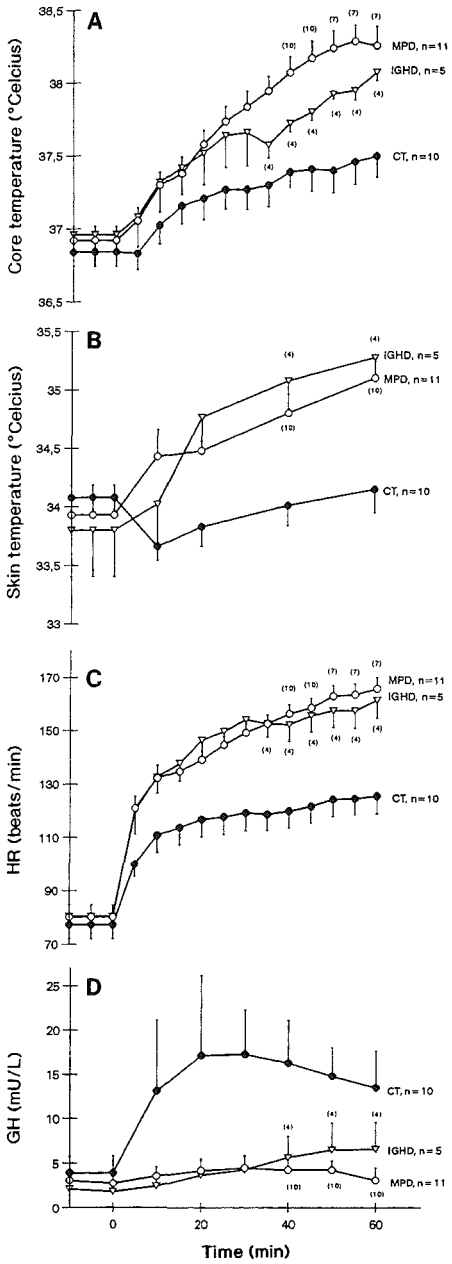

Figure 3 Exercise-induced changes in growth hormone deficient adults with multiple pituitary deficiencies (MPD, O-O) or isolated GH deficiency (IGHD, ▽-▽) as compared to controls (CT, ●-●) in (A) core (oesophageal) temperature, (B) skin temperatures, (C) heart rate and (D) plasma GH levels. The subjects exercised for 60 minutes on a cycle ergometer in a warm environment (35 °C) at a work load corresponding to 45% of VO_2max. Figure from ref [13].

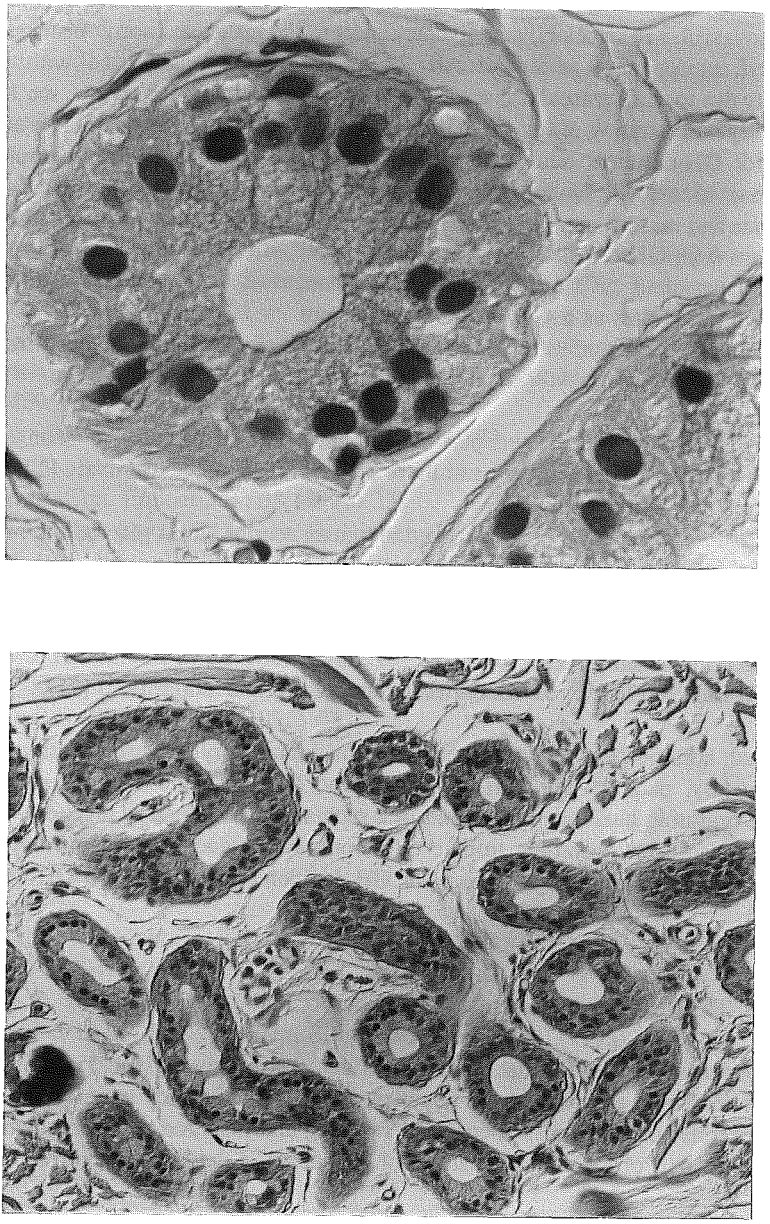

Figure 4 Sections of human eccrine sweat glands at two different magnifications in light microscopy (Hematoxylin-eosin staining). Several tubuli and secretory coils from human eccrine sweat glands are seen (top). Single secretory sweat gland with columnar cells and a few myoepithelial cells (bottom).

GH-deficient patients have a decreased myocardial function, increased abdominal fat mass (a cardiovascular risk factor), atherogenic lipid profile, decreased aortic distensibility and an increased incidence of atherosclerosis. These findings are associated with an increased mortality due to cardiovascular disease in GH-deficient patients (for review, see 16). Increased circulatory strain during exercise due to decreased sweating may constitute an additional risk factor for GH-deficient adults. The impaired thermoregulation during exercise may also predispose to a lower voluntary physical activity contributing to the decreased physical endurance and muscle strength as well as to the increased mortality of cardiovascular diseases in patients with GH-deficiency.

2.2 The human skin as a GH/IGF-I target organ

There are several studies indicating that GH or its mediator IGF-I plays a regulatory role for human skin physiology;

1) GH receptors and GH receptor mRNA have been identified in human eccrine sweat glands by immunohistochemistry and by *in situ* hybridization, respectively [17,18] as well as in cultured skin fibroblasts.

2) IGF-I receptors have been localized in human eccrine sweat glands, although they were primarily present on the myoepithelial cells and in the dermal portion of the eccrine ducts [19].

3) mRNA for IGF binding proteins (especially IGFBP-2 and -4) have been localized in human eccrine sweat glands [20].

4) IGFs and IGFBPs were identified in human skin interstitial fluid [21].

Growth hormone may exert a direct and acute stimulatory effect on eccrine sweat glands. Consequently, patients with GH-deficiency who lack an acute rise of serum GH during exercise or during heat exposure would lack such an acute excitatory response. Alternatively, GH may also exert a chronic trophic effect on sweat gland size, which may have caused atrophy of the eccrine sweat glands in GH-deficient patients before GH replacement is initiated.

3. CONCLUSIONS

In conclusion, it is likely that human skin (incl. eccrine sweat glands) is a GH target organ, and that decreased ability to sweat in patients with GH-deficiency may lead to hyperthermia during exercise or heat stress. Decreased sweating and impaired thermoregulation should be regarded as part of the clinical features of the adult GH-deficiency syndrome.

REFERENCES

1. B. Nielsen, J.R.S. Hales, S. Strange, N.J. Christensen, J. Warberg and B. Saltin. J. Physiol., 460 (1993) 467.

2. K. Sato, W.H. Kang, K. Saga and K.T. Sato. J. Am. Acad. Dermatol., 20 (1989) 713.
3. T.E. Gibson and W.B. Shelley. J. Invest. Dermatol., 11 (1948) 137.
4. K. Main, K.O. Nilsson and N.E. Skakkebæk. Scand. J. Clin. Lab. Invest., 51 (1991) 475.
5. R. Choudhry, M.B. Hodgins, T.H. Van der Kwast, A.O. Brinkmann and W.J.A. Boersma. J. Endocrinol., 133 (1992) 467.
6. S.A. Pedersen, K. Welling, K.F. Michaelsen, J.O. Jørgensen, J.S. Christiansen and N.E. Skakkebæk. Lancet, 8664 (1989) 681.
7. K. Main, K.W. Kastrup and N.E. Skakkebæk. Arch. Dis. Child., 65 (1990) 1380.
8. K.M. Main, D.A. Price, M.O. Savage and N.E. Skakkebæk. J. Clin. Endocrinol. Metab., 77 (1993) 821.
9. L.E. Gibson and R.E. Cooke. Pediatrics, 23 (1959) 545.
10. N. Hjortskov, L.T. Jepsen, B. Nielsen, A. Juul and N.E. Skakkebæk. Clin. Physiol., 15 (1995) 409.
11. A. Juul and N.E. Skakkebæk. Lancet, 338 (1991) 887
12. A. Juul, A. Behrenscheer, T. Tims, B. Nielsen, J. Halkjær-Kristensen and N.E. Skakkebæk. Clin. Endocrinol., 38 (1993) 237.
13. A. Juul, N. Hjortskov, L.T. Jepsen, B. Nielsen, J. Halkjær-Kristensen, N. Vahl, J.O.L. Jørgensen, J.S. Christiansen and N.E. Skakkebæk. J. Clin. Endocrinol. Metab., 80 (1995) 3335.
14. W.-H. Pan, L.-A. Li and M.-J. Tsai. Lancet, 345 (1995) 353.
15. S. Sagawa, K. Shiraki, M.K. Yousef and K. Miki. J. Gerontol., 43 (1988) M1.
16. A. Juul, J.O.L. Jørgensen, J.S. Christiansen, J. Müller and N.E. Skakkebæk, N.E. Hormone Res., 44 (suppl. 3) (1995) 64.
17. P.E. Lobie, W. Breipohl, D.T. Lincoln, J. Garcia-Aragon and M.J. Waters. J. Endocrinol., 126 (1990) 467.
18. S.R. Oakes, K.M. Haynes, M.J. Waters, A.C. Herington and G.A. Werther. J. Clin. Endocrinol. Metab., 75 (1992) 1368.
19. E. Hodak, A.B. Gottlieb, M. Anzilotti and J.G. Krueger. J. Invest. Dermatol., 106 (1996) 564.
20. J.A. Batch, F.A. Mercuri, S.R. Edmondson and G.A. Werther. J. Clin. Endocrinol. Metab., 79 (1994) 1444.
21. S. Xu, S.C. Cwyfan-Hughes, J.W.J. van der Stappen, J. Sansom, J.L. Burton, M. Donnelly and J.M.P. Holly. J. Clin. Endocrinol. Metab., 80 (1995) 2940.

Discussion: The Human Eccrine Sweat Gland: A Possible Growth Hormone Target Organ?

M. Gleeson:

Different normal individuals, show quite a large variation in sweat responses to exercise and to heat, and heavy sweaters tend to have larger sweat glands. Do you have any evidence to show that the gland size is actually smaller in growth hormone deficient subjects?

A. Juul:

I think I can only answer that more or less anecdotally because I have taken almost a hundred skin patches from various patients with growth hormone disorders. We have difficulties in assessing sweat gland size but clearly, just looking at them, it appears that the GH deficient patients have smaller sweat gland acini when compared to controls. However, they also have more subcutaneous fat so when you extract for a microscopy slide they tend to shrink more which makes quantification of the size troublesome.

S. Erill:

Just a comment. It has been known for decades that during sleep the electrodermal resistance, which of course is a function of humidity, changes cyclically along the night. I wonder whether these cycles are coincident with the peaks of secretion of growth hormone?

A. Juul:

I have not seen studies relating precisely to this response to growth secretion during the night. It is known that it is in the phase of REM sleep that the growth hormone is primarily secreted but I do not think that anybody has directly related electrodermal resistance during the night to secretion of growth hormone.

F. Brouns:

Interestingly, high carbohydrate diet and high carbohydrate intake during exercise depresses growth hormone response whereas high fat diet enhances growth hormone response. I know that some work has been done in Copenhagen on high fat diets and high carbohydrate diets. Have you ever considered looking at the differences in sweating rate between subjects, while they are on a light fat diet?

A. Juul:

No, I did not personally, but of course that is very interesting.

P.M. Clarkson:

If you could modify the increase in growth hormone during exercise, then could you also modify the sweating response? We have some preliminary data showing that ingestion of high amounts of glycine increased growth hormone. Might you use something like that to examine whether there is some relationship between GH and sweating?

A. Juul:

We tried to manipulate, in a controlled condition, the growth hormone response to exercise in relation to the sweat response, and as Fred Brouns said, dietary manipulations could be one way. Another way of manipulating the response would be to treat with somatostatin to suppress endogenous growth hormone, and then add exogenous growth hormone versus placebo, but I have no real data on that yet.

D.P.M. MacLaren:

I have a question regarding the use of amino acids in promoting growth hormone. If growth hormone is a banned substance, then we are likely to get to a situation where athletes will be taking amino acids such as glycine or maybe arginine to promote growth hormone. What is the evidence of that happening?

P.M. Clarkson:

Existing evidence is mostly from animal studies using high concentrations. There are some data where amino acids in very high concentrations have been injected, I believe, but very little data with oral administration of amino acids. We did a pilot study, and in a few subjects glycine ingestion showed an increase in GH and in some subjects no change. There are many amino acid supplements that purport to increase growth hormone. However, these claims are largely based on animal data.

T.D. Fahey:

I think the timing might also be critical. The data available on amino acid transport and muscle hypertrophy indicates that this is something that takes many days to manifest. Perhaps the timing of growth hormone stimulation, if it worked at all, might be a very significant factor.

A. Juul:

With respect to timing it is worth noticing that we actually use arginine infusion in children as a way of testing their growth hormone response, and they have usually a very acute rise in response to arginine, within 30 minutes, so it is a very rapid response. The doses used in the clinic with the children are intravenous doses of about 30 grams, whereas the preparations given to athletes contain less than one gram, and most are mixtures.

F. Brouns:

The growth hormone effects are mediated by IGF-I. There are some speculations about giving oral IGF-I by using colostrum. Do you have any idea whether something like that could work or would it be degraded entirely in the gut and not have any effect at all?

A. Juul:

My own feeling is that it would be degraded. I mean, being a peptide it has to be administered systemically.