

COLD EXPOSURE AND HORMONAL SECRETION: A REVIEW

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Low ambient temperature during winter seasons is typical for all circumpolar areas. This sets definite demands for every day life and work. Naked, man is quite helpless in polar winter, but he has been able to inhabit all corners of the earth using technical developments in clothing and housing. Yet there are situations, especially in circumpolar areas, when bodily exposure to cold environment cannot be avoided. Homeothermic animals protect themselves from the cold by increasing heat production and decreasing heat losses. For practical reasons man has very few means of reducing heat loss by natural ways. Heat is produced by muscular work and by chemical reactions. Oxidative phosphorylation of dietary fuels such as carbohydrates and fats brings forward energy-rich phosphate compounds, at the same time liberating heat for bodily uses. Thyroid and adrenal hormones and the sympathetic nerve system maintain and regulate the oxidative phosphorylation that occurs mainly in the mitochondria of brown and white fat and skeletal muscle tissues. It is noteworthy that animals from which thyroid or adrenal glands are removed do not tolerate cold. The efficacy of oxidative phosphorylation has been shown to be regulated by uncoupling proteins (UCP), of which at least 5 species are known at the moment. Adrenal medullary and thyroid hormones and sympathetic stimulation lead to increased activity of uncoupling proteins that reduce the oxidative phosphorylation, by this way increasing heat production. In addition to the increased metabolism, driven by thyroid and adrenal hormones, many changes in cardiovascular functions, such as vasoconstriction and raised blood pressure occur in response to cold. Other humoral factors are related to

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these responses. This review deals with hormonal responses observed in human subjects exposed to cold in various experimental and natural conditions.

THYROID HORMONES

Thyroxine (T4) and triiodothyronine (T3) are iodine-containing hormones secreted from the thyroid gland into blood circulation. Most of the circulating T3 and T4 are bound to serum proteins and only a fraction of them circulate freely. The secretion of T3 and T4 is stimulated by the pituitary hormone TSH (thyroid stimulating hormone) by a feedback mechanism. Thyroid hormones maintain and regulate heat production by stimulation of the expression of the UCPs that leads to increased heat production. Therefore their role in cold adaptation is important (1).

In studies in which healthy lightly-clad subjects are exposed to cold air (5 - 10° C for 30 min to several hours) the serum levels of total thyroid hormones or TSH do not change (2,3). After 80 cold exposures (4° C for 30 min) of after 40 exposures of feet to cold water free and total T3 decreased but no changes were seen in T4 or TSH (4,5). Serum free T4 or free T3 levels in healthy subjects exposed to harsh winter conditions decrease after 15 - 42 wk (6-9). In other similar studies serum free T4 was also shown to decrease and TSH to increase (6). In meat factory workers staying below -20° C for several hours serum total T4 and T3 decreased. In other workers staying daily in temperatures between -10 and 8° C total T4 did not change, total T3 decreased, but unexpectedly free T3 increased (10).

In conclusion, short time exposures to cold air do not cause any changes in serum levels of thyroid hormones or TSH. Long-term exposures to cold air, e.g. in circumpolar climatic conditions, appear to accelerate the consumption of thyroid hormones that firstly manifests as low levels of free T3 and free T4. This may relate to reduced physical and mental performance. Recently, mood disturbances of humans working in Antarctica were found to precede low serum free T3 levels (9) and supplementation with T4 was found to improve cognitive performance (11) This raises the question of whether humans living or working in harsh circumpolar conditions should be treated with thyroid hormones.

ADRENAL CORTICAL HORMONES

Glucocorticoids

The most important glucocorticoid in humans is cortisol, which is essential for life. Cortisol is secreted in response to various stressful situations. Cortisol mobilises glucose, amino acids and fatty acids, increases vascular tone and inhibits allergic and immune reactions. ACTH, a pituitary hormone, stimulates the secretion of cortisol by a feedback mechanism.

The effects of short-time cold air exposure on serum cortisol levels have been studied, some of the results being contradictory. Two-hour-exposure to cold air (5 - 15° C) increased the serum cortisol levels (12,13), and if physical stress and cold water showers were added, the levels increased even more (14). Some studies have reported decreased or (3,15) unchanged in serum cortisol levels (16-18) in response to cold. Exposure to cold air (-5 - - 2° C) during winter seems to make the cortisol levels decrease more slowly than on a warm summer day (19). Prolonged exposure to cold and darkness has also been studied. In some studies, the winter season seemed to have no effect on cortisol levels (20-22), but researchers have also reported increases (6, 7, 23, 24). During polar winter urinary cortisol secretion was free-running and elevated in 2 out of 4 test subjects (25).

The effects of cold exposure on urinary 17-hydroxycorticosteroids, the metabolites of cortisol, have been studied. Exposure to cold air (10° C) for 2 h increased the urinary 17-hydroxycorticosteroid levels (26), but a more severe exposure of -5 - - 2° C did not (19). An Arctic residence of 1 wk increased the urinary 17-hydroxycorticosteroids in native subjects, but not in subjects preadapted to cold (27). A prolonged Antarctic residence increased the 17-hydroxycorticosteroid level (26). In subjects from central Europe annual cortisol secretion seemed to have its acrophase in March (23, 28).

Some studies show that cold exposure has to be longer than 30 min in 4° C to increase the plasma ACTH levels (15, 18,29,30). Exposing subjects for 10 min to 12° C water increased the plasma ACTH (31), whereas prolonged whole body immersion (5° C for 5 - 6 h, mean insulation 1.4 clo) either increased or decreased the ACTH levels

(32). The plasma ACTH did not show a circannual rhythm in subjects from central Europe (24).

Mineralocorticoids

Aldosterone is the main mineralocorticoid of the body. It increases the reabsorption of sodium in the kidneys and regulates fluid balance and blood pressure. The secretion of aldosterone is stimulated by angiotensin II, which is formed by the activity of renin and converting enzyme. Low blood pressure or kidney blood flow stimulates the secretion of renin and finally of aldosterone.

An acute cold air exposure of 4° C for 1 h had no effect on plasma aldosterone, but immersion of hands in 0° C water for only 2 min increased it (33). It appears that water has to be colder than 21° C to have an effect on the plasma aldosterone (34,35). Aldosterone levels seem to be elevated in winter in subjects from France and Japan (22,23).

ADRENAL MEDULLARY HORMONES

The adrenal medulla secretes catecholamines, epinephrine (adrenaline) and norepinephrine (noradrenaline). Norepinephrine is also the transmitter substance of the sympathetic nervous system. Therefore it should be noted that serum norepinephrine originates mostly from the sympathetic nerve endings of vessels. Their secretions are stimulated in response to a number of stressful situations (fight or flight response), exercise, hypoglycaemia, cold, haemorrhage, and hypotension. Increased secretion may also accompany emotional reactions, such as fear, anger, pain, and sexual arousal.

An acute cold air exposure either raised (12,27) or did not have any effect on plasma epinephrine levels (3, 19, 36-38). It seems that exposure has to be more intensive than 3 h in -5° C before it affects the plasma epinephrine. Cold air exposure (1.5 h 4°C) did not have an effect on plasma epinephrine, but when combined with a cognitive task raised epinephrine levels were found (38). It seems that during cold exposures excretion of norepinephrine to urine increases more easily than plasma E (13,19,26).

Whole body (17) or even one hand cold water exposure (39,40) increased epinephrine levels, although some studies did not find any change (33,41). Eating ice cubes in thermoneutral water had no effect on plasma epinephrine (42). Cold exposures related to winter season in a temperate area had no effect on the epinephrine levels (26).

Plasma norepinephrine levels increase in response to thermal stimuli more easily than plasma epinephrine levels. Even a 5-min cold air exposure to 4° C raised plasma norepinephrine (36), although in most studies longer exposure times and lower temperatures have been used (3, 13, 27,37,38,41). Preadaptation to cold helped to keep the norepinephrine levels unchanged (27). Whole body (17,43) or hand exposure to cold water increased the plasma norepinephrine (33,39,40). Even eating ice cubes in thermoneutral water raised the norepinephrine levels (42). A prolonged Antarctic exposure had an increasing effect on plasma norepinephrine levels (26).

GROWTH HORMONE AND PROLACTIN

Growth hormone (GH or somatotropin) and prolactin (PRL) are secreted from anterior pituitary. The secretion of GH is stimulated by hypothalamic GHRH and suppressed by somatostatin. GH exerts direct effects on the metabolism of proteins, carbohydrates, and fats, as well as indirect actions, which result in skeletal growth mediated mostly by insulin-like growth factor I, IGF-I. It increases protein synthesis, decreases plasma amino acid content, and leads to a positive nitrogen balance. Its actions on lipid and carbohydrate metabolism are diabetogenic.

Physical and psychological stress promotes the secretion of GH (anxiety, pain, surgery, haemorrhage, fever, and strenuous exercise). The most important metabolic stimulus for GH secretion is hypoglycaemia. Increased plasma levels of amino acids and reduced plasma levels of FFA stimulate GH output. Oral glucose depresses the release of GH. High plasma GH levels and IGF-I inhibit GH release via feedback action.

GH and PRL bear structural similarities to one another. PRL is weakly somatotropic. It promotes the growth and maturation of the mammary gland during pregnancy and inhibits ovulation. It is under the negative control of dopamine from the hypothalamus. The major stimulus for

prolactin release is the nipple stimulation during suckling. It is also secreted in response to various stresses. Interestingly, the secretion of both GH and PRL appears to be inhibited by cold exposure as discussed below.

A short-term cold air exposure (1/2 - 2 h at 4 - 10° C) either had no effect on the plasma GH levels (16,44) or decreased them (3,30) in male subjects. Sex-related differences have been reported (18). Floating or swimming in cold water had no effect on plasma GH (17,45). Swimming in water over 26° C raised the GH levels (17,46). Intensive cold water exposure, 12° C for 10 min (31), and eating crushed ice in thermoneutral water decreased the plasma GH (42). Neither winter swimming (47) nor a prolonged Antarctic residence had any effect on GH levels (48), perhaps due to lack of intensive body cooling.

An acute cold air exposure of from 15 min to 2 h at 4 - 13° C decreased the plasma PRL levels (3,36,49). In meat factory workers staying daily between -40 and 8° C plasma PRL decreased (10). Exposing face to cold air during bicycle exercise increased plasma PRL less than in controls (50). Winter swimming had no acute effects on plasma PRL but the basal value increased during winter (47). Winter season had no effect (51), or there may be some contradictory sex-related differences in the seasonal rhythmicity of PRL levels (28,52). It appears that cold exposure has to be severe enough to result in decreases in the secretions of GH and PRL.

REPRODUCTIVE HORMONES

The male androgenic hormone is testosterone secreted by Leydig cells. The female hormones are estrogen and progesterone secreted by the ovarian cells. Testosterone, oestrogen and progesterone together with anterior pituitary gonadotropins, FSH and LH, regulate the maturation and release of spermatozoa and ova.

In females clear surges of FSH, LH and estrogen occur at ovulation. During the second half of the ovarian cycle, the luteal phase, the major steroid hormone secreted by the corpus luteum is progesterone.

Meat factory male workers exposed to environmental temperatures between -40 and - 8° C daily during their

daily working days had normal FSH and LH levels (10), but were wearing adequate cold clothing. Neither acute exposure to 12° C water for 10 min (31) nor winter swimming had any effect on serum FSH in men (47). Basal FSH levels seemed to have its circannual acrophase in February in men (23), and in women in May-June and November-December in follicular and luteal phases, respectively (53). Acute cold air exposure for 2 h in 10° C had no effect on serum LH levels in men (3). The annual secretion of LH had its acrophase in March (23) and in November-December in men and women (luteal phase), respectively (53).

In male subjects testosterone showed no change in responses to acute or mild repeated cold air (3,10). Only meat factory workers exposed daily to extreme cold (-40° C), showed a decrease in their serum testosterone levels (10). Annual testosterone secretion had its acrophase in October (23,54), although in one study no annual changes were observed (53).

The effect of cold air exposure on serum estradiol levels has only been tested in female meat factory workers exposed daily to temperatures between -40 and - 8° C. Estradiol seemed to decrease in those workers (10). The annual secretion of estradiol had its trough in February-March in women during the luteal phase (53). It is possible that increased luminosity during that time had a greater effect on gonadotropins and sex steroids than environmental temperature.

POSTERIOR PITUITARY HORMONES

Vasopressin (ADH or antidiuretic hormone) and oxytocin are synthesised by hypothalamic neurons and stored for secretion in the posterior pituitary gland. They are structurally similar but have different actions. ADH stimulates the reabsorption of water from nephrons, thereby decreasing urinary volume and increasing urinary osmolality. It exerts a pressor effect on vascular smooth muscle and is released in response to an increase in the osmotic pressure of the plasma or a fall in blood volume. Patients with abnormally high ADH levels have highly concentrated urine, with water retention, lowered plasma osmolality, and sodium depletion. Lack of ADH leads to diabetes insipidus. Oxytocin stimulates the ejection of milk. It increases the contractile activity of the uterine myometrium and may

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play a role in the expulsion of the fetus during labour. It is released in response to suckling. Oxytocin deficiency results in failure to breast-feed. Excessive oxytocin secretion has never been demonstrated. The effects of cold air/water exposure on ADH or oxytocin levels have not been studied.

MELATONIN

Melatonin is an indole hormone secreted by the pineal gland. Environmental luminosity is the main regulator for melatonin secretion (55). There are no studies performed in human subjects in which melatonin secretion is measured in association with cold exposures.

PANCREATIC HORMONES

Insulin is synthesised by the β -cells of the pancreatic islets of Langerhans and secreted in response to a rise in plasma glucose and amino acids. It stimulates the uptake and utilisation of glucose by cells particularly in liver, adipose tissue, and skeletal muscle, thereby causing a fall in plasma glucose. It stimulates glycogen and protein synthesis. A lack of insulin or of insulin receptors gives rise to diabetes mellitus in which there is hyperglycaemia leading to polyuria, excessive thirst, and weight loss.

Glucagon is the most potent hyperglycaemic hormone. It is secreted by the α -cells of the islets and acts to promote the release of glucose into the blood. It acts in antagonism to insulin to provide short-term regulation of plasma glucose. Hypoglycaemia is the principal stimulus for the secretion of glucagon which then stimulates glucogenolysis, lipolysis, and gluconeogenesis.

Floating in cold water had no effect on serum insulin (17), but swimming in thermoneutral water decreased serum insulin (17,45). Also a cold shower of 10° C after a strenuous exercise (14) decreased serum insulin. Repeated swimming in the winter (2 - 10 min at 2 - 6.8° C) decreased both basal and stimulated insulin levels (47).

The effects of cold water exposure on serum glucagon levels have only been looked at in one study. It has been found out that floating in water decreased the serum glucagon only if the water was colder than 27° C. Also swim-

ming decreased the glucagon levels only if the water temperature was over 21°C (17). Cold air exposure has been observed to result in a rapid rise in plasma glucagon while the level of insulin remained unaltered (56).

VASOACTIVE HORMONES AND SUBSTANCES

The endothelial cells of blood vessels secrete vasoactive substances: prostaglandins, thromboxanes, nitric oxide (NO), C-type natriuretic peptide (CNP) and endothelins. These are divided into vasoconstrictors and vasodilators. Circulating vasoconstrictor hormones include vasopressin (AVP), norepinephrine (NE), epinephrine (E) and angiotensin II. Vasodilator hormones include kinins, vasoactive intestinal polypeptide (VIP), and A- and B-type atrial natriuretic peptides (ANP, BNP).

Vasoconstrictors

Endothelin I, the most potent vasoconstrictor, is produced from its precursor, big endothelin-I. Small amounts of endothelin-I are secreted into blood, but most of it is in the media of blood vessels and acts in a paracrine fashion. Its secretion is stimulated by angiotensin II, catecholamines, growth factors, hypoxia, insulin, high-density lipoprotein (HDL), shear stress and thrombin, and inhibited by NO, ANP, prostaglandin E₂, and prostacyclin. Endothelin I may play a role in the pathophysiology of congestive heart failure and myocardial infarction. Angiotensin II is a vasoconstrictor, formed from angiotensin I. It helps to maintain blood pressure. The formation of angiotensin II is increased by the fall in blood pressure or the reduction in extracellular fluid (ECF) volume. Angiotensin II may be important in clinical hypertension.

Thromboxane A₂ is secreted by platelets and promotes platelet aggregation. AVP is a vasoconstrictor, but when it is injected into normal individuals, there is a compensating decrease in cardiac output, so that there is little change in blood pressure. The noradrenergic postganglionic sympathetic nerves on blood vessels contain neuropeptide Y (NPY), which inhibits the effects of vagal stimulation. NE has a generalised vasoconstrictor action whereas E dilates the vessels in skeletal muscle and the liver.

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Cold air exposure of 10° C for 2 h had no effect on plasma endothelin-I levels (57), but immersion of one hand in cold water increased the plasma endothelin-I (58). Plasma angiotensin II levels did not change during a 1-h cold air exposure of 4° C or when hands were immersed in 0° C water for 10 min (33). Cold air exposure of 4° C for 30 min decreased the plasma vasopressin levels (15). The effects of cold exposure on thromboxane A2 or on neuropeptide Y have not been studied.

Vasodilators Natriuretic peptides ANP and BNP are secreted from heart atria and ventricles. They are diuretic, natriuretic and cause vasodilatation. Their secretion is stimulated by stretching of cardiac muscle. NO is synthesised from arginine in a reaction catalysed by nitric oxide synthase (NOS). Tonic release of NO is necessary to maintain normal blood pressure. NO deficiency may be related to hypertension. NO may also be involved in the pathogenesis of atherosclerosis. Acetylcholine, bradykinin, VIP, substance P (SP), histamine and prostacyclin act via the endothelium and dilate blood vessels.

Cold air exposure of 10° C for 2 h increased the plasma ANP levels (57). A 40-min period of whole body cooling did not change the plasma level of NO, but some seasonal variation was detected with a higher level of NO in the winter than in the summer (59). The effects of cold exposure on histamine level have not been studied in healthy subjects and other vasodilators have not been studied at all.

CONCLUSIONS

The major hormonal responses to various cold exposures are summarised in Table I.

As seen from table I, several experimental conditions still exist in which the effects of cold exposure on hormonal secretions are not known, and the results in which no changes have been documented may not be true. In those studies only daytime hormonal responses to cold have been reported. However, several hormones, such as pituitary hormones, adrenal cortical hormones, testosterone and melatonin, are mainly secreted during the night. Therefore there is room for studies to chart the effects of cold on the day and nighttime secretion profiles of hormones. The different effects of short and long-term cold

Table I. The effects of cold exposure on human hormone secretion

Hormone	Short-time cold exposure	Cold season
Thyroid gland		
Serum T4	no change	no change
Free T4	no change	decreases
Serum T3	no change	decreases
Free T3		decreases
Adrenal cortex		
Cortisol	increases	increases
Aldosterone	increases	increases
Adrenal medulla and nerve endings		
Epinephrine	no change	no change
Norepinephrine	increases	increases in hypertensive patients
Pituitary gland		
ACTH	increases	
β-endorphin	decreases	
FSH	no change	increases
LH	no change	increases
GH	decreases	no change
PRL	decreases	no change
ADH	decreases	
TSH	no change	increases
Pineal gland		
Melatonin		
Pancreas		
Insulin	no change	increases
Glucagon	increases	
Vasoactive hormones		
Angiotensin II	no change	
Endothelin-I	no change or increase	
ANP	increase	

exposures should also be studied and their consequences as to normal physical and mental performance clarified. This is clearly shown in the studies of Palinkas et al. and Reed et al. (9,11), who demonstrated that long-term Antarctic exposures will be manifested in reduced thyroid function followed by mood and cognitive disturbances. What was most interesting, these disturbances could be alleviated with a supplementation of thyroid hormones (11).

We also need an exact method by which the intensity of the cold exposure can be determined. This would be possible by a personal thermometer with a data logger fastened e.g. to the outside and inside of clothing. This would solve the problem of clothing, too.

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Another important matter is the role of cold-induced hormonal changes as risk factors in diseases or working life. The studies presented here do not offer direct information about that. We know that daily 5-8 h outdoor work in the circumpolar climatic conditions of northern Finland will reduce serum free T3 (6). Other studies also show that low thyroid hormone levels may lead to mood disturbances (9). The submaximal work rate in humans working for 11 months in Antarctic conditions decreased significantly (11). Short-term cold exposures are experienced as inconvenient, if the mean skin temperature decreases below 31°C or heat losses exceed over 4 kJ/kg body weight (60). In most of the studies referred above the heat loss has clearly exceeded the limit of 4 kJ/kg, and therefore the cold-induced negative subjective feelings and reduced sensomotor control might have impaired mood and working. Further studies are required to determine the significance of cold-induced hormonal responses in these disturbances.

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