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Endocrine and Metabolic Changes during Exhaustive Multifactorial Military Stress. Results from Studies during the Ranger Training Course of the Norwegian Military Academy

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INTRODUCTION

The endocrine and metabolic system is strongly affected by stress and its regulation is vital for both physical and mental performance particularly during physical stress, energy deficiency and sleep deprivation. In the present paper we have studied the endocrine and metabolic changes in male cadets from the Norwegian Military Academy during a strenuous military training course.

THE EXPERIMENTAL MODEL

All experiments were performed in male cadets from the Norwegian Military Academy during their ranger training courses at the end of the first year (June) or beginning of the second year (August-September) at the Academy. The course is part of the cadets' obligatory training program at the Academy. In spite of this we were allowed to do some standardization of the training program and to introduce differences between groups in order to study the impact of different stress factors. The cadets were between 21 and 28 years of age and physically well trained and healthy.

The courses normally lasted from 5 to 7 days. The cadets had continuous physical infantry activities around the clock corresponding to 35 % of their maximal oxygen uptake (Waldum and Huser 1974, Aakvaag et al 1978a) as measured by continuous heart rate recordings.

The work load corresponded to a daily energy consumption of 34.000 to 46.000 KJ, which is in accordance with the estimated energy loss during the course. The total weight loss depended on the food supply during the course. In the middle of the course each cadet got a half hen contains 2500 to 3400 KJ mainly in the form of proteins and was often the only food they received. For these cadets the weight loss reached 8-12 kg during the course. However, in some courses, the cadets consumed as much as 4200-6300 KJ daily in the form of bread, biscuits and other carbohydrate sources, which prevented some of the weight loss during the course, in particular loss of muscle proteins and glycogen reserves. From calliper measurements and needle biopsies the estimated fat loss is 3-4 kg during the course (Rognum et al 1982).

The cadets were normally not allowed any organized sleep during the course except for the cadets participating in a 7 day course who got 3-4 hours of sleep on day 5. From heart rate recordings, from wrist actigraphy (Vitalog) and from our own and officers' observation, the cadets' sleep during the course has been estimated to 1-3 hours totally.

BLOOD SAMPLING

Blood samples were taken by venipuncture in the antecubital vein, whereas repeated sampling was performed through an indwelling plastic cannula also in the antecubital vein. The blood was drawn into pre-chilled vacuum tubes containing the necessary anticoagulants, such as EDTA or heparin, or also substances necessary to conserve the hormones investigated, such as the peptidase inhibitor aprotinin. The blood for preparation of plasma was centrifuged immediately in a refrigerated centrifuge for approximately 20 minutes, and the plasma

was frozen at -80 °C on dry ice. Blood for preparation of serum was allowed to clot at room temperature for 30 minutes before centrifugation. The samples were kept at - 80 °C in an ultrafreezer until analyzed.

BIOCHEMICAL ANALYSIS

Catecholamines in plasma were analyzed using a radioenzymatic method (s-adenosyl methionin as a tritiated methyl donor transferred to the amines by catechol-o-methyl transferase), which is a modification of the method of daPrada and Zürcher (1976). Total concentration of catecholamines was analyzed with the same method after desulphatation of the sulphate group by a sulphatase (Sigma S-1629). The plasma concentration of the conjugated catecholamines was calculated by subtracting the concentration of the free amines from the total concentration of catecholamines in blood. All the other hormone analyses were performed with radioimmunoassays with commercial kits, the methods and antibodies or radiolabeled tracers are described in the different papers. Glucose was analyzed with three different methods, first the hexokinase method (Boehringer), then by an oxygen sensitive electrode (Beckmann Analyser 2), and lastly by the Kodak Ektakem DT2 system.

STATISTICAL ANALYSIS

Since our experiments often include serial samples from the same persons, such as every morning, or responses to different types of stimulation, we had to use an analysis of variance for repeated measures. The data were analyzed by means of commercial statistical programs such as SPSS (Manova) or BMDP (4V, 5V, 8V). If the requirements for normal distribution or equal variance were not satisfied, the results were transformed by logarithmic transformation or analyzed with non-parametric methods. However, since the non-parametric methods are rather few and without possibilities to treat many groups in a repeated analysis the parametric methods were preferred. Student's t-test has been used to identify significant differences.

RESULTS AND DISCUSSION

The catecholamines and adrenergic receptors

Catecholamines are important regulators of homeostasis and are indispensable for adequate physiological responses to different environmental conditions and demands such as exercise, fasting, cold stress, surgery, and diseases (von Euler 1974, Unger et al 1980, Kuchel et al 1986, Landsberg and Young 1992). The adrenal medulla is the only source for adrenaline, whereas noradrenaline has a dual origin. Two third of circulating noradrenaline derives from the sympathetic nervous system and the rest from the adrenals. In addition to a small adrenal secretion of dopamine, plasma dopamine derives mainly from the sympathetic ganglion interneurons where dopamine is assumed to be a transmitter. Physical exercise stimulates the release of noradrenaline more than adrenaline, whereas the opposite is the case for mental stress and hypoglycemia (von Euler 1974, Åkerstedt et al 1983).

The role of the conjugated plasma catecholamines has been a matter of dispute. In humans the conjugated amines are mainly sulphated, and there are high concentrations of the phenol-sulpho-transferase in the liver, in the gastro-intestinal tract and in blood platelets, and the plasma levels of conjugated amines increase after ingestion of amine-rich food. Sulphatation might therefore be the body's protection against food amines which could, if they were absorbed unchanged, induce dramatic changes in blood pressure and pulse frequency and cause anxiety and catabolic stress (Mielke and Strobel 1994). Fig. 2, 3, and 4 shows that conjugation does not serve to inactivate catecholamines after short term exercise, since there is no increase in the conjugated amine levels in the recovery period after the bicycle exercise test. Since the cadets did not ingest any significant amounts of nutrients during the course, the only source for the increased plasma levels of conjugated amines during the course had to be sulphaconjugation of free circulating amines. Sulphaconjugation therefore serves to inactivate catecholamines during prolonged exercise. Conjugated amines do not serve as a source for the free catecholamines during exercise, since there was no decrease in the conjugated catecholamines simultaneously with the increase in the free amines. Large interindividual variations have been found for the plasma conjugated catecholamines, particularly for dopamine. During the ranger course this large interindividual variation disappeared, which indicates that the variations are due to the ingestion of food that contains different amounts of amines.

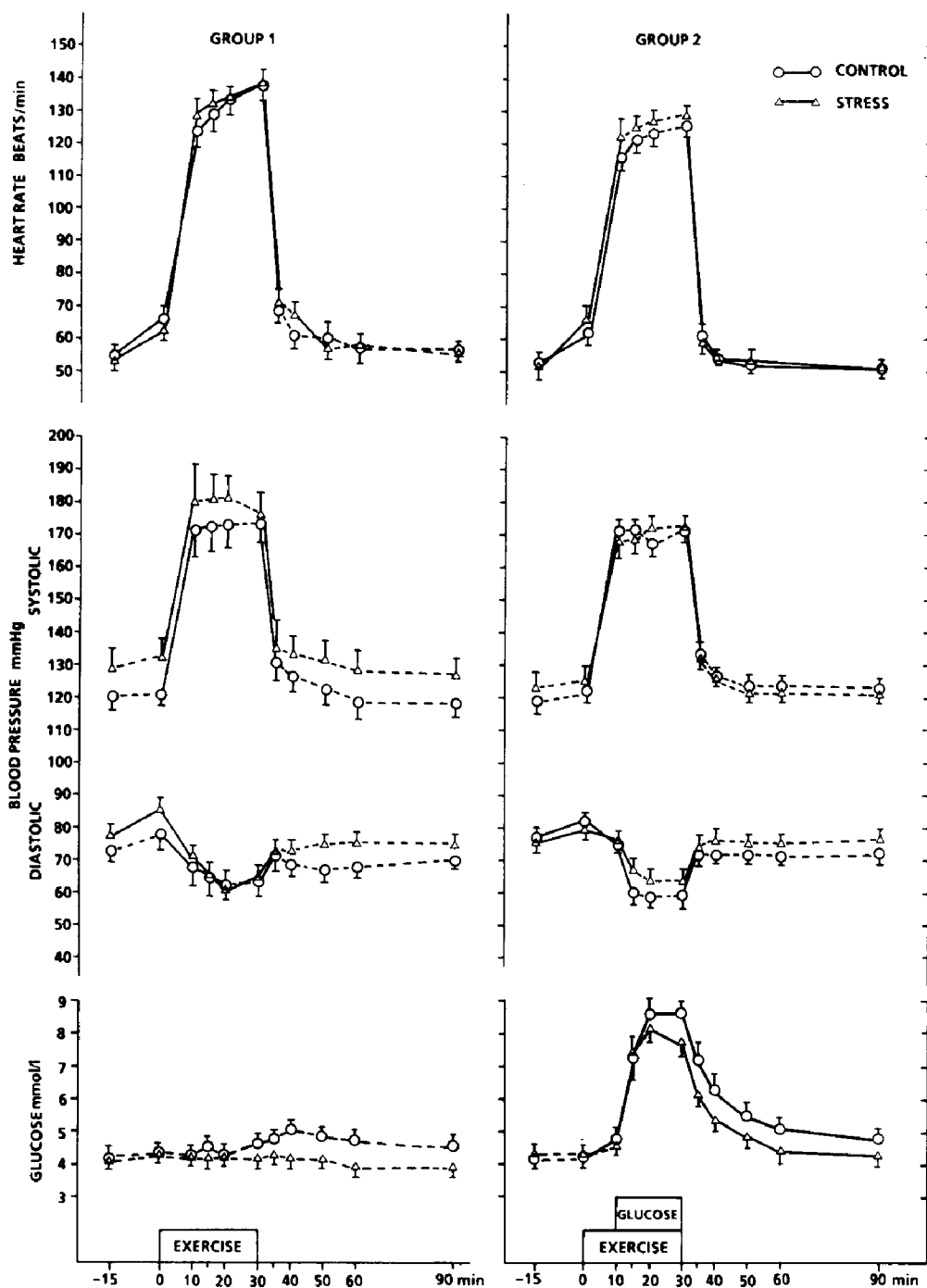


Fig. 1. The pulse rate, blood pressure and plasma glucose responses to 30 min ergometer exercise with approximately 60% of VO_2max in a control experiment and after a 5-day ranger training course with heavy physical exercise combined with energy and sleep deprivation. In contrast to Group 1 the subjects of Group 2 received 25 g of glucose intravenously during the last 20 min of exercises. The levels are presented as means and the vertical bars represent the standard error of the mean. Point to point variations significant at $P < 0.01$ are indicated by thick lines.

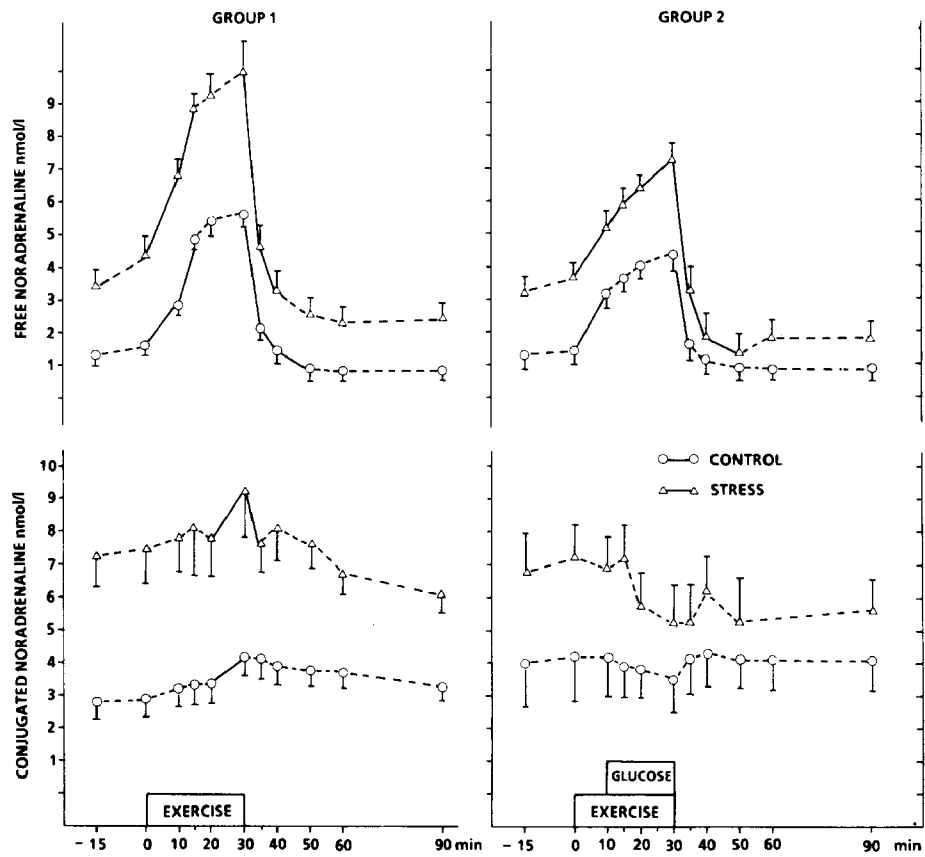


Fig. 2. Plasma levels of free and conjugated noradrenaline. For details, see Fig. 1.

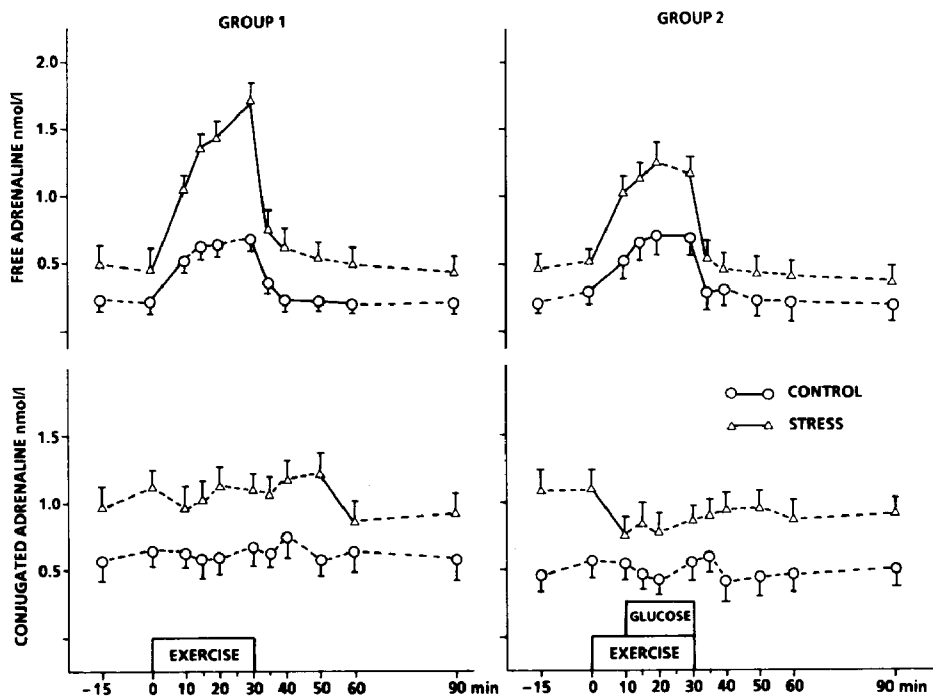


Fig. 3. The plasma free and conjugated adrenaline. For details, see Fig. 1.

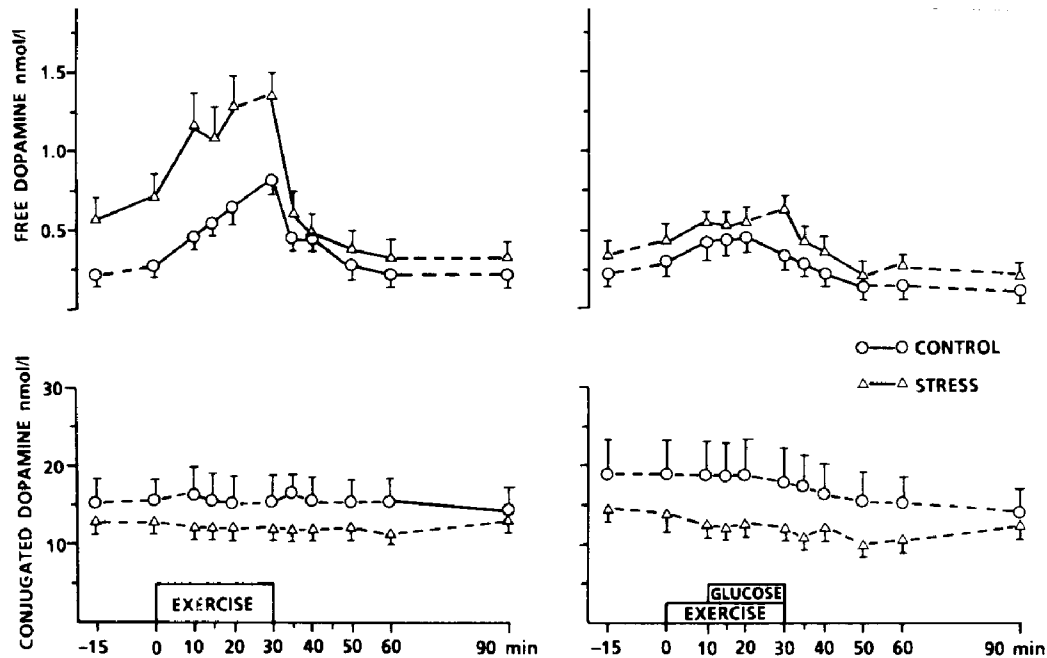


Fig. 4. Plasma free and conjugated dopamine. For details, see Fig. 1.

Ahlquist (1948) classified the adrenergic receptors as α and β , based on the rank order of potency of the different catecholamines in the vascular beds. The receptors have further been classified into α_1 , α_2 , β_1 , β_2 , D_1 and D_2 adrenoceptors, based on ligand-binding studies and responses to synthetic agonists and antagonists (Hoffman and Lefkowitz 1992a, b). The α_1 receptor is postsynaptic and located on the effector tissues such as vascular smooth muscle. Stimulation of this receptor may cause vasoconstriction, increased peripheral vascular resistance and increased blood pressure, pupillary dilation and intestinal and urine bladder relaxation. In contrast many α_2 receptors are located presynaptically and their stimulation inhibits the noradrenaline secretion. α_2 -receptor stimulation decreases sympathetic nerve activity and causes aggregation of platelets (Keiser 1995). β_1 -adrenoceptor stimulation causes positive inotropic and chronotropic effects in the heart, lipolysis and increased renin secretion by the kidney. Stimulation of the β_2 receptor causes bronchodilation, vasodilatation particularly in the skeletal muscle, glycogenolysis, smooth muscle relaxation and increased release of noradrenaline from sympathetic nerves. Adrenaline is a much more powerful stimulant of the β_2 receptor than noradrenaline, whereas they have approximately equal potency at the β_1 and α_2 receptor. For the α_1 receptor, noradrenaline is the most powerful stimulator. Dopamine is a weak stimulator of the α and β receptors, and in addition it has its own receptor, the D_1 receptor, which induces vasodilatation in the coronary, renal, mesenteric and cerebral vascular beds. Stimulation of the D_1 receptor in the kidney causes natriuresis and diuresis. This may be a mechanism for the natriuresis and diuresis during the first days of starvation. D_2 -receptors are located presynaptically in the sympathetic nerve endings, and their stimulation inhibits release of noradrenaline and sympathetic ganglion transmission. Stimulation of the dopamine receptors in the brain causes emesis and inhibition of prolactin release. The decreased prolactin levels during the course from rather high precourse levels may be due to dopamine inhibition of prolactin secretion. Both dopamine receptors mediate their effects through the adenylate cyclase. With high catecholamine levels for prolonged periods of time, such as in patients with pheochromocytoma, a desensitization may occur by several mechanisms; internalization of receptors, decreased binding affinity of the receptor on the cell surface, uncoupling of the receptor and decreased sensitivity of the adenylate cyclase activity (Keiser 1995). The present investigation demonstrates an adrenergic desensitization during prolonged stress in that both pulse rate and blood pressure and their responses to short term physical exercise are almost unchanged in spite of considerably increased plasma catecholamine responses (Opstad et al 1980, Fig 1, 2, 3 and 4). This is well in accordance with the decrease in the leukocyte adrenergic receptors during the course (Fig 5). The high correlation between increased plasma catecholamines and reduced number of adrenergic receptors indicates a homologous down-regulation during the course. In contrast, the increased number of adrenergic receptors at the end of the course might be explained by a heterologous upregulation, because corticosteroids, which are

increased during the course, are known to stimulate the synthesis of adrenergic receptors. Thyroid hormones are also known to stimulate the synthesis of adrenergic receptors which should have given the opposite results, since all thyroid hormones decrease during the course (Opstad et al 1984). Another mechanism which may explain the increased catecholamine levels, is decreased reuptake into sympathetic nerve terminals, which is the main mechanism for noradrenaline inactivation. Decreased reuptake in sympathetic nerve terminals is probably the reason for increased noradrenaline responses to stress in aged people (Esler et al 1995).

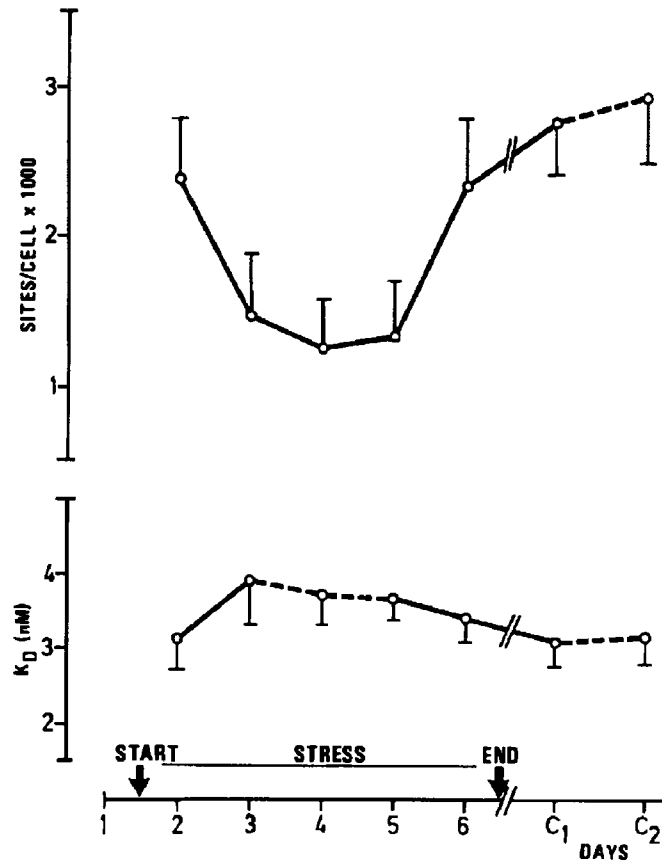


Fig. 5. The upper curve shows the total number of HBI-sites on mononuclear cells each day during the ranger training course with heavy physical exercise, energy and sleep deficiency. C₁ and C₂ are the control values obtained several weeks after the course. Values are given as means and SEM. Day to day variations statistically significant at $P < 0.01$ are indicated by thick lines and not significant changes by dotted lines. The dissociation constant K_d is shown in the lower curve.

Fig 7 shows that the adrenergic desensitization during the course is not only due to reduced number of adrenergic receptors, but is also due to reduced adenylate cyclase activity, in that the cAMP response to adrenaline stimulation was reduced during the course, both in its sensitivity and its maximal response (Opstad 1990, 1991). The adrenergic desensitization seems to be due to the prolonged physical exercise, since there was minimal effects of sleep or food deprivation on the catecholamine responses to bicycle exercise during the course. One explanation for this is that the effect of exercise dominated over a small effect of food or sleep deficiency. However, there was a surprisingly small effect of glucose infusion on the plasma catecholamines during a bicycle exercise test (Fig 2 and 3), since it is known that particularly adrenaline is very sensitive to decreased plasma glucose levels (von Euler 1974). High stress levels and associated hormones have traditionally been associated with unfavourable survival rate. More recently it has been shown in a population study that low resting plasma adrenaline levels were associated with an unfavourable survival rate (Christensen and Jensen 1994).

The increased catecholamine responses to bicycle exercise shows that there was no sign of exhaustion in the sympathoadrenal nervous system during the course, and that the mechanism for decreased performance is to find in a desensitization of the peripheral tissue to nervous and hormone stimulation. During prolonged stress with high turnover in the sympathoadrenal system it has been proposed to give supplements of tyrosine, the precursor in the synthesis of catecholamines, to prevent exhaustion (Ahlers et al 1994, Liebermann 1994). There was no indication of such a need during the ranger course of 5-7 days since there was no deficiency in the cadets' catecholamine response to exercise.

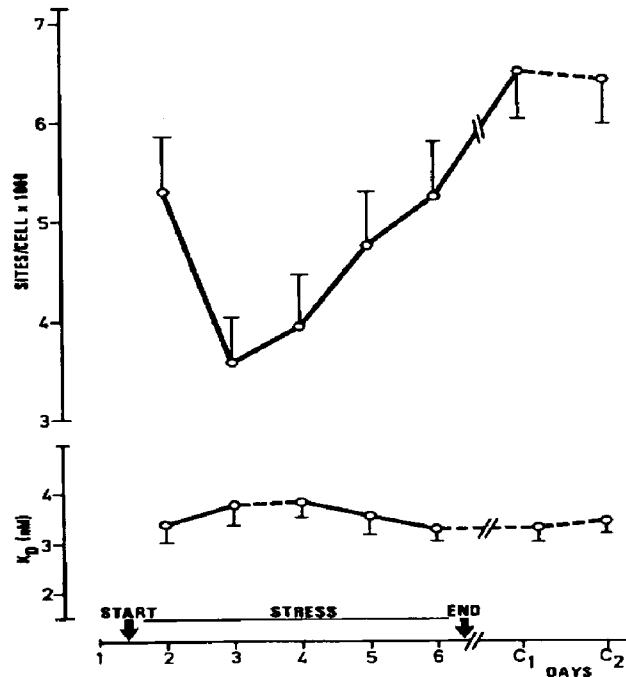


Fig. 6. Total number of HBI-sites, and values for the dissociation constant K_d for granulocytes during the ranger training course. For detail see Fig. 3.

Catecholamines normally do not pass the blood-brain barrier. The possible action of plasma catecholamines in the CNS therefore has to be through locations where the blood brain barrier is fenestrated. Most often this is in the basic parts of the brain, particularly in the hypothalamus. However, there is no information on possible effects of circulating catecholamines on the CNS. During an adrenaline or noradrenaline infusion test lasting for 20 minutes during the ranger training course a striking clinical difference was observed between the two hormones, in that the subjects given adrenaline became very alert, and stayed awake in spite of prolonged sleep deprivation. In contrast the subjects given noradrenaline got drowsy and tended to fall asleep. If this effect was mediated via increased plasma glucose levels, the same effects should have been observed in subjects given glucose intravenously. Since adrenaline does not pass the blood-brain barrier, it is tempting to suggest that this effect is due to secondary mechanisms. In the brain, noradrenaline serves as neurotransmitter for the neurones in the locus coeruleus, which have a widespread distribution of their fibres through most of the brain.

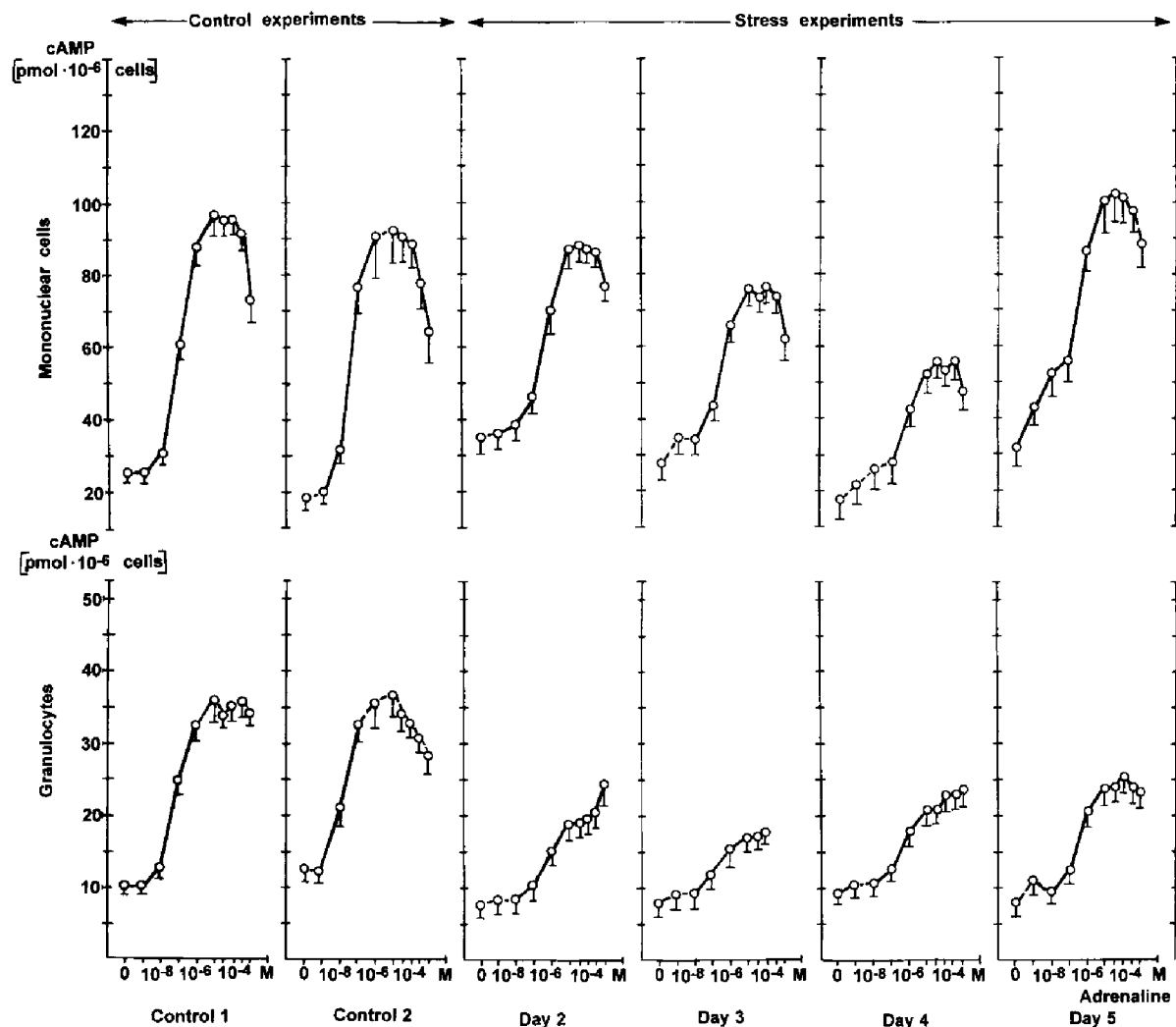


Fig. 7. Cyclic adenosine monophosphate (cAMP) response to adrenaline stimulation in human mononuclear cells and granulocytes during a 5-day military training course with heavy physical activities, sleep and energy deficiency. The experiments were performed on days 2-5 and in two control experiments performed while the cadets had normal activities at the training Academy. The results are shown as means and SEM. Time to time variations statistically significant at $P < 0.01$ are shown with thick lines.

ADRENAL STEROIDS

The hypothalamo-pituitary-adrenocortical activation was considered by Selye as a main physiological reaction to stress with the following shrinkage of the thymus, spleen, lymphatic structure and deep bleeding ulcers in the stomach and upper gut. The anti-inflammatory effects of the glucocorticoids were in opposition to the disease of adaptation of Selye and were therefore not recognized for decades (Selye 1946, Munck and Náray-Tóth 1995).

The adrenal cortex can be divided in 3 separate zones, the zona glomerulosa which produces the mineralocorticoids, zona reticulosa which produces the glucocorticosteroids and zona fasciculata which produces the adrenal androgens (Parker 1989, 1995). There are no sharp distinctions between the different zones, and in addition there is considerable crossreactivity in their physiological effects, and there is to some extent an interconversion of the different steroids in the peripheral tissues, particularly in the liver and in fat tissue but lately also demonstrated for muscle tissue. The mineralocorticoids are mainly regulated by the renin-angiotensin axis, but are also stimulated by ACTH. Glucocorticoids are almost exclusively regulated by ACTH, whereas adrenal androgens beside ACTH may also be stimulated by a polypeptide isolated from the pituitary that is different from ACTH, however, this is still under debate (Parker 1995).

The 4-5 fold increase in the plasma levels of aldosterone during the course is mainly due to reduced intake of food and by that the intake of NaCl. However, NaCl/K excretion is strongly regulated, and by a 90 % decrease in the urine excretion of NaCl, plasma levels of NaCl were maintained constant. When extra food was given containing approximately 20 g/24h of NaCl for each cadet, both plasma renin activity and aldosterone levels were reduced by more than 50 %, but still the salt excretion from the kidneys was reduced by 50 % compared to normal (Opstad et al 1985b, Opstad et al 1994). Clinically only a few cadets showed symptoms of salt deficiency, and only in connection with exercise and high environmental temperature. Therefore, in spite of the very strong regulation of salt balance by the kidney, occasionally small extra challenge was sufficient to cause clinical symptoms of hyponatremia.

The increase in glucocorticoids during the course is due to a combination of physical exercise and energy deficiency. During the bicycle exercise test the plasma cortisol levels were lower both during the exercise test and during recovery in the well fed subjects. To rise the plasma levels of cortisol in rested subjects the exercise has to last for at least 60 minutes and at more than 60 % of maximal oxygen uptake (Sundsfjord et al 1975). However, during the course this rise starts earlier and at lower exercise intensity (Opstad et al 1980). It is well established that cortisol stimulates energy mobilization at many levels. First of all cortisol stimulates gluconeogenesis through the stimulation of relevant hepatic enzyme systems. In addition cortisol mediates its action through the stimulation of the synthesis of adrenergic β -receptors, making adrenaline more efficient. Thereby cortisol counterbalances the stress-induced homologous downregulation of the β -receptors and is an important mechanism for preventing adrenaline from losing its efficiency during prolonged exhausting stress. This will contribute to maintain physical as well as mental performance capacity. Cortisol may also contribute during prolonged physical strain to minimize all inflammatory processes which might be painful and which might prevent soldiers from performing their tasks. Cortisol passes the blood brain barrier and influences a number of brain functions such as mental performance and memorization (Funder 1991). The antiinflammatory response may sometimes even be lifesaving, since it prevents the inflammatory process from being harmful for the body.

In contrast to glucocorticoids and mineralocorticoids, which increase during the training courses, there is a decrease in the adrenal androgens such as dihydroepiandrosterone, androstendione and 17α -OH progesterone (Fig 8). ACTH is known to stimulate the adrenal secretion of all steroids. The decrease found for ACTH levels could then well explain the decreased secretion of adrenal androgens. However, ACTH levels measured do not necessarily reflect the mean level of ACTH stimulation of the adrenals. To avoid testing the acute effects of exercise, but rather a steady physiological state, the cadets were not allowed any significant exercise just before testing or blood sampling. The problem with this experimental procedure is that the subjects during the course are rarely in a steady state situation but are rather in a state of activation or in a state of recovery. In the present case ACTH, which has a short half life of only some minutes, therefore recovers faster than cortisol, which has a half life of approximately 90 minutes. During this period cortisol will, in addition, exercise a negative feedback on ACTH production which is stronger than normal and by consequence lead to lower plasma ACTH levels than normal. So in spite of the measured ACTH levels, ACTH may well be responsible for the increased cortisol levels. ACTH will also contribute to the increased aldosterone levels but in combination with an even stronger and more important regulator, the renin-angiotensin system (Parker 1995). In contrast to the free adrenal androgens, the sulphated form, dihydroepiandrosterone-sulphate (DHEA-S) which circulates in the plasma in micromolar concentration and with a half life of several days, increases during the course (Fig 8). This is probably due to increased secretion from the adrenals and therefore shows that the adrenal gland may differentiate its secretion of the different androgens or steroids. The increased levels of DHEA-S might also originate from peripheral sulphatation of the free androgens, or there may even be a combination of the increased secretion and peripheral sulphatation of free androgens. Our original hypothesis that increased adrenal androgens could compensate for effects of decreased testicular androgens is not verified. This is also supported by the hypogonadic clinical symptoms during the course such as almost no beard growth, reduced muscle strength and less aggressive behaviour. It is presumed that a main reason for the decreased adrenal androgens during the course is the physical strain particularly during night time. However, the decrease of unconjugated adrenal androgens found during sleep deprivation by Åkerstedt et al (1980) may indicate that also sleep is important to preserve the increase in adrenal androgens during night time.

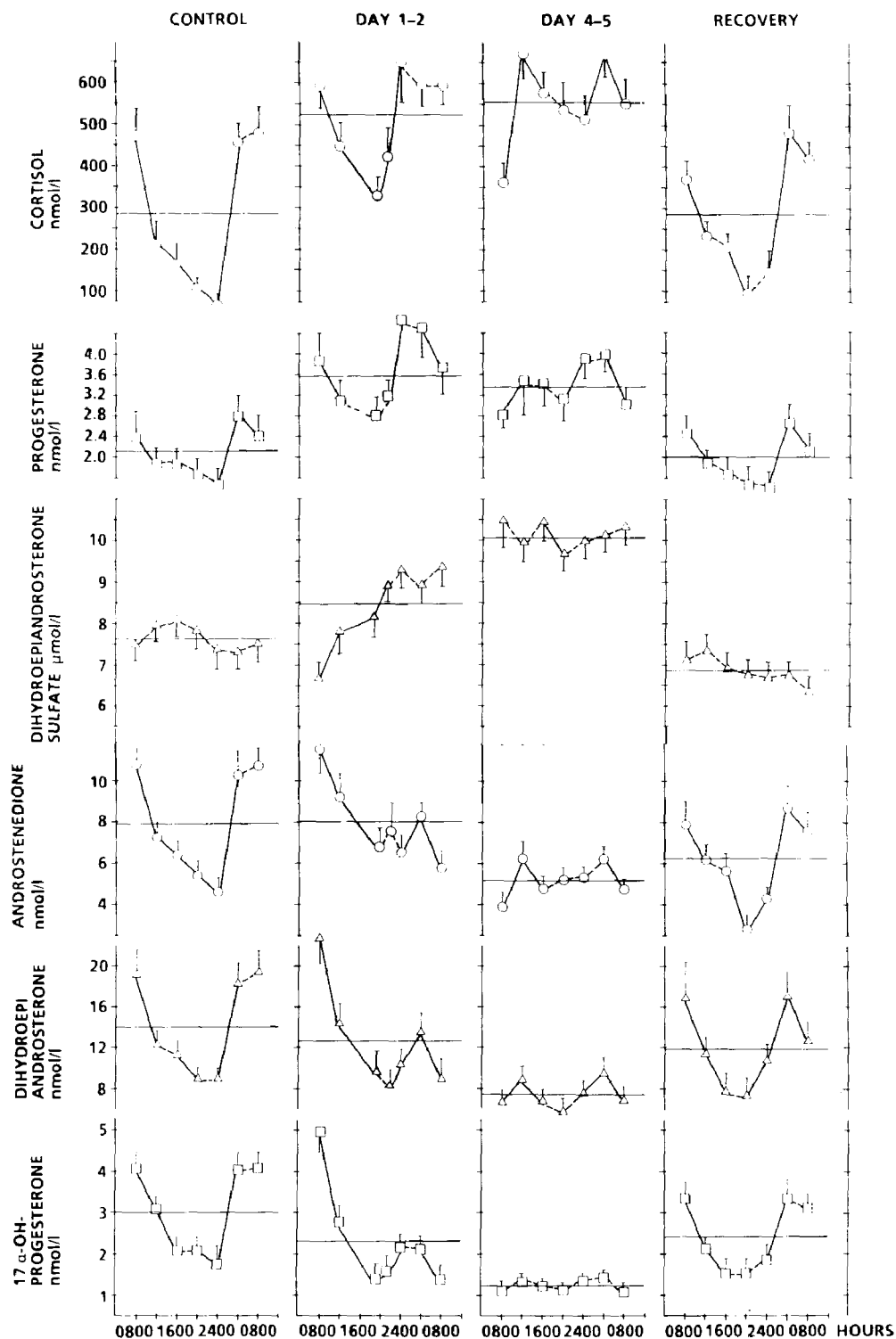


Fig. 8. The circadian rhythm for Cortisol, progesterone, dihydroepiandrosterone sulfate, androstenedione, dihydroepiandrosterone and 17 α -hydroxyprogesterone during a control experiment with normal school activities (left column), during the first 24 h of continuous activities (mid-left) and from 72 to 97h of activities (mid-right) during a military training course with continuous physical activities almost without sleep and with limited amounts of food. The recovery experiment (right column) was performed 4-5 days after the course, while the cadets had normal school activities. The blood samples were collected at 4 hrs intervals. The results are expressed as means $\pm$ sem. The time to time variations that were statistically significant at $p < 0.01$ are shown with thick lines and those that were not significant by dotted lines. Horizontal lines indicate 24-h means.

Like all other free steroids, the glucocorticoids pass the blood-brain barrier and are known to influence behaviour, mood, neuronal excitability and electrical activity. Behavioural changes are observed both in excess states such as Cushing's disease and in deficient states such as Addison's disease. Sleep disorders are often associated with glucocorticoid therapy (McEwen 1979). Adrenalectomy leads to the loss of neurones in the hippocampal formation, particularly in the dentate gyrus (Sapolsky et al 1991), whereas very high levels of glucocorticoids have been shown to cause the death of hippocampal CA3 pyramidal cells and to potentiate neuronal death evoked by toxic substances (Packan and Sapolsky 1990, Stein-Behrens et al 1992, Munch and Náray-Fejes-Tóth 1995).

Glucocorticoid receptors are widely distributed in neurones and glial cells throughout the brain (Funder 1991, Power et al 1991), whereas the mineralocorticoid receptor is mainly localized in the hippocampus and septum. In spite of the fact that mineralocorticoid receptors have a lower affinity for the glucocorticoids than for aldosterone, this is compensated by far higher concentrations of glucocorticoids. There are small areas where the mineralocorticoid receptor is protected against glucocorticoid effects by 11β -hydroxysteroid dehydrogenase and is by that aldosterone selective. In the limbic structure mineralocorticoid receptors mediate glucocorticoid effects. Studies in hippocampal slices have shown that low concentrations of glucocorticoids, when only the mineralocorticoid receptors are activated, give enhanced neuronal excitability. In contrast, high concentrations which activate the glucocorticoid receptors, suppress hippocampal excitability (Jöels and De Kloet 1989, Kerr et al 1989). In addition to the electrophysiological effects, glucocorticoids inhibit glucose transport in hippocampal neurones and glial cells, they affect glycerol-phosphate dehydrogenase (McCarthy and deVillis 1980) and glutamine synthetase in astrocytes (Hellermyer et al 1981) and induction of K^+ channel mRNA synthesis and channel expression in pituitary cells (Levitan et al 1991).

Also the adrenal androgens pass the blood brain barrier, but in contrast to the glucocorticoids, mineralocorticoids and testosterone, the cerebral concentration of pregnenolone, DHEA and their sulphate and fatty esters is considerably higher than in plasma. In addition the sulphate and fatty acid esters do not cross the blood brain barrier, and it has been shown that their variations are independent of the plasma variations. It is also shown that the oligodendrocytes have the enzymes (Cytochrom P-450) necessary to convert cholesterol to $\Delta 5$ - 3β -OH androgens and their conjugated and lipid derivatives. Moreover, DHEA and its sulphate persisted for several weeks after pharmacological or surgical glandular suppression. This contrasts with testosterone, glucocorticoids and mineralocorticoids which disappear in the brain after the removal of their respective glands, and which normally have lower concentrations in the brain than in plasma (Corpéchet et al 1983, Denner et al 1990, Akwa et al 1991, 1992, Robel et al 1991, Vourch et al 1992). As for plasma steroids, brain steroids show a rather strong circadian rhythm with the highest levels during the dark period. The acrophase of corticosterone in plasma preceded the acrophase of brain DHEA and pregnenolone, indicating an independence between plasma and brain steroids. DHEAS has been shown to interact with rat forebrain membrane γ -amino butyric acid (GABA) receptor complex as a non-competitive negative neuromodulator. The GABA receptor is an oligomeric protein complex that, when activated by an agonist, produces an increase in neuronal membrane conductance to Cl^- ions, resulting in membrane hyperpolarization and reduced neuronal excitability (Chavatal and Kettenmann 1991, Demirgoron et al 1991, Robel et al 1991). Thus, adrenal androgens cause neuronal excitation and regulate neuronal and glial growth *in vitro* (Carette and Poulain 1984, Bologna et al 1987, Muntwyler and Bologna 1989), and also affect memory and aggressive behaviour in mice (Young et al 1991, Flood et al 1992). Pregnenolone, DHEA and DHEAS have also been found in the peripheral nerve tissue and might be trophic factors for these nerves (Akwa et al 1991, Chvatal and Kettenmann 1991, Demirgoron et al 1991, Morfin et al 1992). Nasman et al (1991) have shown that plasma DHEAS was decreased in patients with Alzheimer's disease. Morris et al (1987) have shown that concentration of gonadal and adrenal androgens is related to female libido. Plasma adrenal androgens show a peak concentration in the third decade of life, and then decrease gradually to very low levels in senescence. A decrease is also found for gonadal androgens with ageing with considerable interindividual alterations, however, the decrease is far less pronounced than for the adrenal androgens (Zumoff et al 1982, Davidson et al 1983, Tenover et al 1987a, b, 1988, Swerdloff and Wang 1993a, b, Winters 1995). In contrast to the androgens, the classical stress hormones, the glucocorticoids, the catecholamines, and the other counterregulatory hormones increase with age (Landsberg and Young 1992, Munck and Náray-Fejes-Tóth 1995). It has been speculated whether the hormonal alterations may be one of the mechanisms behind the

process of ageing. In this case the demonstrated alterations found during stress will promote the process of ageing. However, since “adrenal androgens” probably do not have the same source in brain and plasma, and since we and others have not investigated the effect of stress on brain androgens, we do not know exactly the possible consequences for the central nervous system of alterations in these hormones.

TESTICULAR ANDROGENS

The testicular androgens are steroids that are responsible for the development of the male phenotype. They have three main effects: stimulation of masculine sexual characteristics, anabolic function by stimulating the increase of muscle mass, and influence on behaviour, particularly by stimulating initiative and aggressiveness. Plasma testosterone derives for 95 % from the testis, and is its most important and potent androgenic hormone. The rest (5%) derives from conversion of androgen precursors to testosterone in peripheral tissue and also for a very small part from direct adrenal secretion (Catlin 1995, Handelsman 1995, Hiipakka and Shutsung 1995, Kretser et al 1995).

Androstenedione and dihydroepiandrosterone are also secreted from the testis but at rather low rate. Their biological effects are small, but they may serve as precursors for the peripheral synthesis of testosterone or oestrogens. The androgens affect the development, growth and function of a wide variety of tissues and cell types by their interaction with the intracellular androgen receptor. Androgen-receptor complexes bind to specific sequences of DNA and modulate the rate of specific gene transcription (Kretser et al 1995). The biological effects of androgens in different tissues are determined by the tissue concentration of androgen receptors and also by the tissue concentration of the enzyme 5α -reductase which converts testosterone to dihydrotestosterone which has a 5 times higher affinity for the androgen receptor than testosterone. Tissues containing androgen receptors include the reproductive organs, brain, kidney, liver, skin, skeletal muscle, cardiac muscle, bone, larynx, thymus, hematopoietic and lipid tissue. Although a small portion of 5α -dihydrotestosterone (DHT) is secreted from the testis, most of the circulating DHT derives from peripheral metabolism of testosterone in various tissues. The tissue sensitivity to androgenic hormones is also dependent on the tissue content of 5α -reductase, which is necessary for the conversion of testosterone to dihydrotestosterone, since this enzyme may convert androgens to the most potent androgen DHT (Hiipakka and Shutsung 1995).

During the ranger training course there is a dramatic decrease in the plasma levels of both free and total testosterone and dihydrotestosterone. The nocturnal increase in the plasma levels of testosterone was completely abolished during the course, showing that night activity is even more deleterious for anabolism and recovery than day activity (Fig 9).

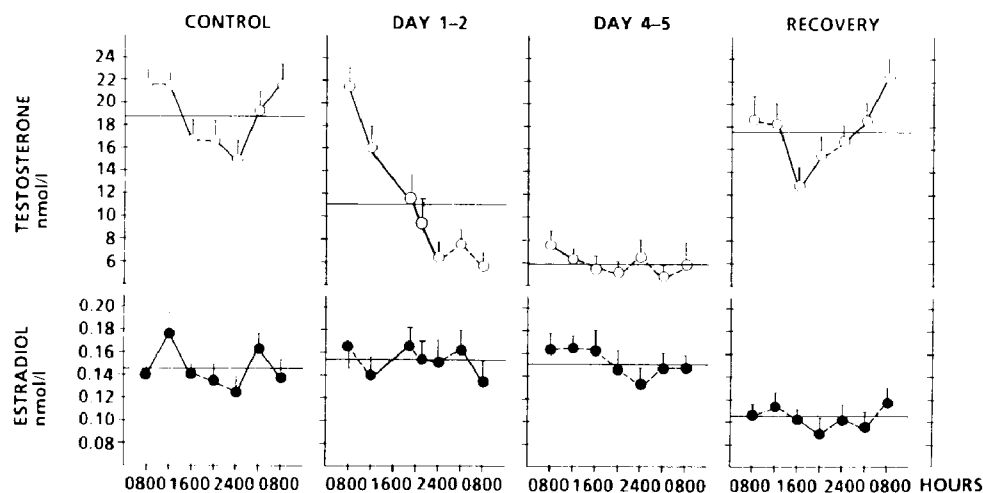


Fig. 9. Alterations in the circadian rhythm for testosterone and estradiol in a control experiment, during short and prolonged continuous stress and during recovery. For details, see Fig. 8.

The decrease in dihydrotestosterone probably reflects the decrease in androgen precursors since the percent decrease in testosterone and dihydrotestosterone are similar. From the present results we do not have any indication of alterations in the 5 α -reductase activity in androgen target tissues during the course.

The decrease in testicular androgens was mainly due to the physical strain since no significant effect was found when the cadets were given extra food. A slower decrease was seen in subjects given 3 hours of extra sleep each night, however, all cadets reached the same level on the last day of the course (Opstad and Aakvaag 1982, 1983, Elias and Wilson 1993). Others have shown that extra food might reduce the decrement shown to take place for testosterone during a military training course (Guezennec et al 1994). The present papers also show that the decrease in testosterone is due to reduced secretion of LH/FSH. Further the increased LH/FSH response to GnRH stimulation indicates that there is a reduced hypothalamic GnRH secretion during the course leading to an increased sensitivity of the LH/FSH producing cells to GnRH stimulation. This shows that androgen secretion during the course is regulated from the hypothalamus and its inputs from other brain areas.

The clinical signs of reduced androgen activity are present since the beard growth during the whole course corresponds to a normal growth of one day, and this beard growth takes mainly place during the first day of the course. This corresponds well to the alterations in the androgen hormones. During the course the cadets become less aggressive, show less initiative, become more defensive and depressive, which is also in accordance with the alterations in the plasma levels of androgens (Opstad et al 1978, Myhrer 1987).

Like other steroids, testosterone and dihydrotestosterone may cross the blood brain barrier and bind to cerebral androgen receptors. Androgen receptors are mainly localized in the medial preoptic area, bed nucleus of the stria terminalis, amygdala, hippocampus, thalamus and several hypothalamic nuclei including the periventricular nuclei, supraoptic, and ventromedial nuclei and median eminence. In addition there are androgen receptors in other areas of the brain such as the frontal cortex etc., but these areas have lower receptor densities than the classical sites (Wortsmann et al 1987, Sar et al 1990, Jones and Pfaff 1991, Takeda et al 1991, Genazzani et al 1992, Burgess and Handa 1993, Menard and Harlan 1993, Clancy et al 1994). In addition androgens may act through the oestrogen receptor since aromatase irreversibly transforms testosterone to oestradiol and androstendione to oestrone. This enzyme was originally found in ovary and placenta, but has also been localized to the mammalian brain particularly in the medial preoptic area, septal region, the bed nucleus of the stria terminalis and the tuberal hypothalamus (Balthazart and Foidart 1993, Hutchison 1993). The "limbic-telencephalic" aromatase-immunoreactivity is shown to be independent of gonadectomy, whereas the hypothalamic aromatase-immunoreactivity disappears after gonadectomy (Jakab et al 1993). Occupation of oestrogen receptors in the male brain is dependent on brain aromatase activity, whereas the occupation of oestrogen receptors in the female brain is more dependent on circulating oestrogen particularly during the preovulatory oestrogen surge. In addition both oestrogen and androgen receptor concentrations decrease after gonadectomy and reappear after substitution and are further increased by anabolic steroid abuse (Sar et al 1990, Takeda et al 1991, Menard and Harlan 1993, Catlin 1995). Dihydrotestosterone has a 4-5 times higher affinity for the androgen receptor than testosterone, and tissue sensitivity for testosterone may therefore be quite dependent on the tissue concentration of 5 α -reductase which converts testosterone to dihydrotestosterone. Tissues such as the external genitalia and accessory sex glands have high concentrations of 5 α -reductase, and congenital deficiency in this enzyme causes female external genitalia. However, the significance of this enzyme in the brain sensitivity for androgens is less investigated. In contrast, aromatase has been shown to be necessary for the sexual differentiation of the fetal brain in rats and also for the adult (Kalra and Kalra 1991, Swerdloff et al 1992, Hutchison 1993, Jacob et al 1993). Abuse of anabolic steroids promote aggressiveness and motivation which might be an important contribution to increased performance (Moritani and DeVries 1979, Catlin 1995). A positive correlation has also been found between aggressiveness and blood testosterone levels during puberty, and adulthood in prison population, adolescent boys and military veterans (Hines and Green 1991). Testosterone is also shown to decrease with ageing, and some look upon aged men as androgen deficient and believe that reduced testosterone levels are responsible for asthenia, decreasing muscle mass, osteoporosis, and decreased sexual activity (Swerdloff and Wang 1993a, b, Winters 1995).

The protein wasting during physical stress is probably also enhanced by the decrease in the plasma androgens. However, in contrast to the decreased beard growth, which is a rather specific androgenic effect, the protein wasting and alteration in behaviour are not specific and therefore have additional explanations. Although sleep deprivation affects testosterone secretion, there are a multitude of other mechanisms that are responsible for the behavioural consequences of sleep deprivation, and the decrease in testosterone is only one of them. The most important reason for protein wasting is probably the state of fasting during the course with lack of carbohydrates and proteins and an extremely high and continuous need for energy. Although there was no significant effect of fasting on plasma androgens during the course, it has been shown by others that fasting may affect plasma androgen levels. It has been speculated whether the cadets' combat performance, such as aggressiveness, initiative and muscle strength could be improved by giving the cadets androgens. However, the "wisdom of the body" might indicate that high androgen activity is incompatible with a high energy production. Androgens in such extreme conditions could disturb this mechanism and force the body to take the energy from other more critical sources for survival than the tissues containing androgen receptors. This might be a very hazardous experiment. In contrast, androgens could probably ameliorate or shorten the cadets recovery period if the androgen substitution is combined with an adequate diet.

THYROID HORMONES

Thyroid hormones have a myriad of physiological functions and induce alterations in almost all metabolic pathways and organs (Dumont and Vassart 1995, Jameson and deGroot 1995, Nicoloff and LoPresti 1995, Refetoff and Nicoloff 1995, Sarne and Refetoff 1995). Thyroid secretion is mainly regulated by thyroid stimulating hormone (TSH) through the hypothalamo-pituitary axis (Wilber 1995). Thyroid hormones increase oxygen consumption, affect protein, carbohydrate, lipid and vitamin metabolism. These hormones also interact with a number of other hormones, peptides and growth factors so that many of their effects occur through interaction with other endocrine systems. The main effects of thyroid hormones on metabolism and cellular differentiation, development and growth are closely interrelated and represent a complex integration of pathways both at the cellular level and in terms of whole body physiology. Many of the developmental effects are not reversed by later treatment with hormones, suggesting that thyroid hormones act in combination with other differentiation factors that may not be available later in life. Clinically alterations in thyroid hormones were long the basis for the measurement of basal metabolic rate or oxygen consumption which are increased in hyperthyroidism and reduced in hypothyroidism. Measurement of oxygen consumption in individual tissues has shown that the metabolic effects of thyroid hormones on oxygen consumption are highly variable in different organs and tissues with marked effects in the heart, skeletal muscle, liver, kidney and gastrointestinal organs, whereas the brain, spleen and gonad tissues are metabolically less responsive. The pituitary gland shows paradoxical response since there is increased metabolic activity in hypothyroidism and reduced activity in hyperthyroidism. These variable tissue responses are partly due to tissue presence of receptors for thyroid hormones. Oxygen consumption is, however, not a marker of thyroid hormone effects in all tissues. This is for instance the case for thyroid hormone effects in the brain which shows one of the most pronounced clinical effects of hypo- and hyper-thyroidism. Most of the effects of thyroid hormones are now considered to occur through the actions of nuclear receptors that cause alterations in gene expression. The thyroid stimulation of energy production also leads to increased heat production which will ameliorate the cadets' cold tolerance (Jameson and deGroot 1995). During the ranger course there is an increase in oxygen consumption both at rest and during work in spite of the decreased levels of thyroid hormones (Bahr et al 1991).

All plasma thyroxin (T4) derives from thyroid secretion, whereas only 5-10 % of T3 and 1-3 % of rT3 derive from thyroid secretion. The rest originates from peripheral conversion of T4, mainly in the liver. Only 0.02 % of T4 and 0.3 % of T3 circulate in the free form, the rest is bound to plasma proteins such as thyroxin binding globulin (TBG), thyroxin binding prealbumin (TBPA) and albumin. Nuclear receptor saturation of 75 % in the brain and pituitary and 50 % in liver and kidney in spite of a plasma concentration of 2×10^{-11} M for T4 and 6×10^{-12} M for T3 versus a dissociation constant for the thyroid receptor of 2×10^{-9} M for T4 and 2×10^{-10} M for T3 indicates active transport mechanisms across plasma membranes. This is supported by the fact that for instance the concentration of T3 is 50 times greater in the erythrocytes than in plasma (Osty et al 1990, Nagashima et al 1993, Jameson and deGroot 1995).

Clinical observation of the cadets during the ranger training course showed that all had symptoms of hypothyroidism, since they shivered, were easily freezing, had slow motions and were also mentally slower than normal. The thyroid studies performed showed a decrease in thyroid hormones corresponding to the half life of T4 (Aakvaag et al 1978a, b, Opstad and Aakvaag 1981, 1983). An initial increase during the first day (12 hours) of activities was due to exercise, whereas the following decrease corresponding to the half-life of T4 was due to energy deficiency. The plasma concentration of rT3 also increased during the first day of activities due to exercise, but continued to increase during the course due to energy deficiency. This finding is well in accordance with the decreased plasma levels of thyroid hormones during fasting or starvation (Palmlblad et al 1977, Jung et al 1980). There were no corresponding alterations in the plasma levels of thyroid stimulating hormone (TSH) during the course (Fig 11). Surprisingly the cadets that were allowed 3 hours of sleep each night showed the strongest decrease in TSH, whereas energy deficiency, which caused the difference in thyroid hormones, caused only moderately higher TSH levels. This is well in accordance with later published data on the inhibitory effect of sleep on TSH (Opstad et al 1984, Parker et al 1987).

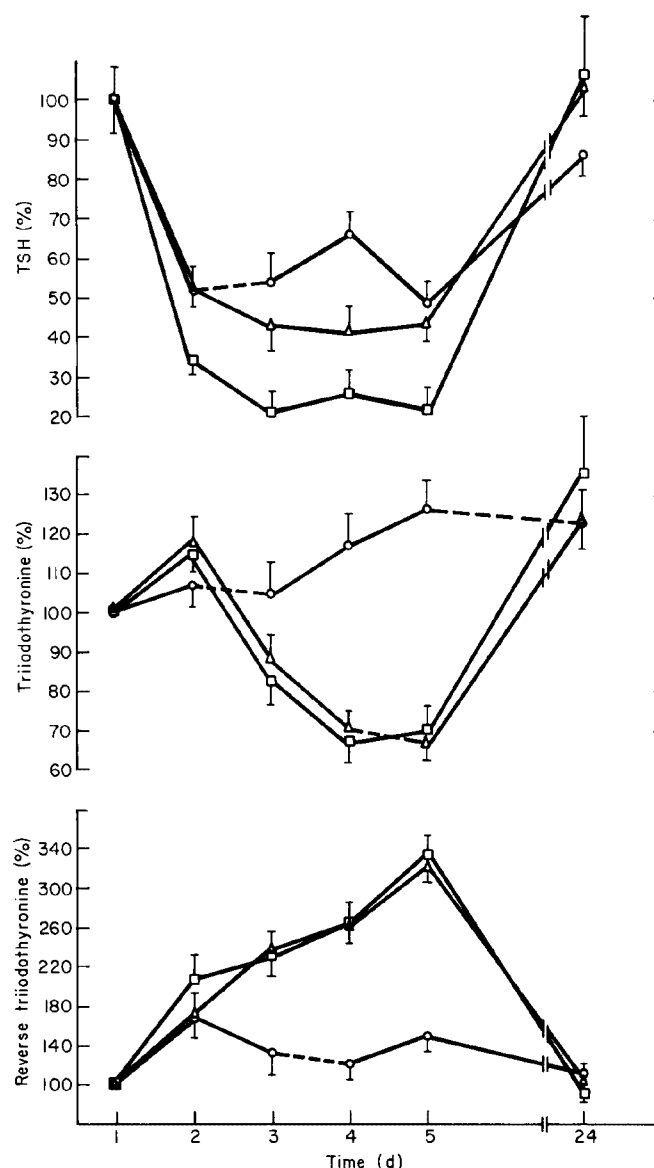


Fig. 10. The percentage changes in the serum concentrations of TSH, T3 and rT3 during a 5 d ranger training course with heavy physical activities, energy deficiency and sleep deprivation. The subjects are divided into 3 groups; Group 1 (n=9) (Δ) that was both sleep- and energy deprived, Group 2 (o) that was compensated for the energy deficiency and Group 3 ($\square$) that was allowed 3 hours of sleep each night. The day to day variation statistically significant at $P < 0.01$ is shown by a thick line. The levels are given as means and the vertical bars represent the standard error of the mean.

Most hormones show circadian rhythm. The long half-life of thyroid hormones will mask a possible circadian rhythm. In the present work no significant circadian rhythm was demonstrated for thyroid hormones in spite of the presence of a circadian rhythm for TSH. The circadian rhythm of TSH showed a maximum level at midnight before the other hormones and the lowest level in the afternoon. In addition to decreased TSH levels in plasma, prolonged continuous stress also gave an extinguished circadian rhythm, which was re-established after 4-5 days of recovery. In light of the present results one might believe that some deterioration of mental and physical performance might be due to alterations in thyroid hormones and that these alterations might be reversed by adequate food supply during the course (Pasquini and Adamo 1994). There are indications that the conversion of T₄ to T₃ in the liver is dependent on carbohydrate metabolism, and that optimal nutrition during prolonged physical strain must contain a certain critical amount of carbohydrates to maintain thyroid hormones at a sufficient level in order to preserve mental and physical performance, and in our climate preserve the soldiers' cold tolerance.

The cadets' hypothyroidism may contribute to the explanation of many of the alterations in both mental and physical function during the course, since hypothyroidism may lead to slowing of all movements and mental function, decreased alertness and vigilance, loss of ambitions and impaired memory. There may be cognitive impairment which may reach dementia. Hypothyroid patients often sleep longer than normal, may become anxious and depressed (myxedema madness) (Swanson et al 1981). Speech is slow, hesitant and hoarse, and physical movements are clumsy. Contraction and relaxation phases of reflexes are prolonged. Paresthesia, sensorimotor neuropathies, cerebellar dysfunction, ataxia, intention tremor and nystagmus may also appear but are reversible when thyroid hormone levels are normalized (Swanson et al 1981, Beghi et al 1989, Osterweil et al 1992, Utiger 1995). Myalgia, muscle cramps, muscle stiffness, weakness and increased fatigability are common and pseudohypertrophy and pseudomyotonia of the muscles may develop with increased plasma levels of serum creatin kinase, lactate dehydrogenase and aminotransferase. Muscle fiber enlargements with oedema, loss of striation and sarcoplasmic degeneration, arthralgia, and joint stiffness due to synovial thickening are also described (Khaleeli et al 1983, Utiger 1995). The decreased thyroid function during the course may also contribute to impaired heart and lung function and to the gastrointestinal symptoms in the form of nausea, vomiting, decreased intestinal motility with constipation and abdominal distension (Ladenson et al 1992, Utiger 1995). The hypothyroidism may also contribute to the decreased haemoglobin levels during the course (Lindemann et al 1978, Tachman and Guthrie 1984) and may cause increased bleeding time, decrease in clotting factors and abnormal platelet function (Rogers et al 1982). The overall morbidity or mortality is not increased in hypothyroid patients, although some postoperative complications are more frequent, such as hypotension, cardiac failure, gastrointestinal dysfunction, and drug clearance is prolonged (Weinberg et al 1983, Ladenson et al 1984, Drucker and Burrow 1985). The decreased thyroid function during the course may also contribute to the decreased set-point temperature during the course.

INSULIN AND GLUCOSE METABOLISM

Glucose homeostasis is important for both human mental and physical performance. Plasma glucose is therefore strongly regulated by a variety of hormones. Insulin is, however, the only hormone able to reduce plasma glucose concentration, whereas a multitude of hormones may increase plasma glucose levels. These hormones are called the counterregulatory hormones and are the catecholamines, glucagon, human growth hormone, glucocorticoids and peptides such as VIP (for review see Kahn and White 1995, Polonsky and O'Meara 1995). Plasma glucose is regulated both by a direct effect of glucose and its metabolites in the β -cells of the pancreas and via its influence on the hypothalamic structure via the autonomic nervous system. The neurotransmitters influencing the β -cells of the pancreas are acetylcholine, noradrenaline, GABA, and different peptides such as somatostatin, VIP, etc. Also circulatory catecholamines may influence insulin secretion from the pancreas since the β -receptors stimulate and α -receptors inhibit insulin secretion from the β -cells (Keiser 1995). At high catecholamine concentrations the α -receptor dominates over the β -receptor and this might be one of the factors explaining the decrease of plasma insulin during exercise. During a bicycle exercise test, plasma glucose was shown to increase, whereas a decrease was seen during the same exercise test during the ranger course (Opstad et al 1980, Rognum et al 1981, Opstad 1987). This is probably explained

by the depleted glycogen depots and that the glycogenesis is too slow to compensate for the absence of muscle and liver glycogen during the course.

An impaired glucose tolerance was also observed during the course mainly due to the physical strain, whereas extra sleep or extra food did not reverse the impaired glucose tolerance (Fonnum and Opstad 1983, Opstad unpublished). The mechanism for this decreased glucose tolerance is a combination of lower insulin responses in combination with peripheral insulin resistance. The insulin response to glucose is normalized within 3-5 hours, whereas the peripheral insulin resistance subsides well beyond this time. The decreased insulin response to glucose is not due to adrenergic inhibition of the insulin secretion since α -blockers did not reverse the decrease in insulin secretion (Opstad unpublished). The practical consequences of these findings is that the cadets during or after the course are advised to eat small meals particularly as carbohydrates are concerned.

PITUITARY HORMONES

Human Growth Hormone (hGH) stimulates protein synthesis as well as energy mobilisation. Energy mobilisation favours lipolysis, whereas the uptake of glucose in working muscles is inhibited by hGH, probably by decreasing the insulin sensitivity. This effect of hGH is increased during starvation (Møller et al 1993). This also leads to an increased insulin response to glucose ingestion and impaired glucose tolerance. These changes may, however, also be mediated by the increased levels of plasma free fatty acids stimulated by hGH. Increased hGH levels may therefore contribute to the glucose intolerance observed during the course. The rapid metabolic actions of hGH, such as lipolysis, promotion of glucose and amino acid transport across membranes, are probably mediated through the hGH receptor directly. In contrast, many of the growth promoting actions of hGH are mediated through the intermediate action of insulin growth factor 1 which is mainly synthesised in the liver (Vanderschueren-Lodeweyckx 1993, Weltman et al 1994, Daughaday 1995). hGH release from the liver is balanced between the stimulation by growth hormone releasing hormone (secreted from the nucleus arcuatus) and the inhibition by somatostatin (secreted from the paraventricular nucleus/ optic nucleus) both released from the hypothalamus and transported to the pituitary gland by the portal circulation. Many stimuli of hGH secretion such as exercise, hypoglycaemia, proteins (arginine) and l-Dopa act through an α -adrenergic mechanism and are inhibited by α -adrenergic receptor blockers such as phentolamine, and are potentiated by the β -adrenergic blocker propranolol. Other neurotransmitters such as CCK, VIP, opioid peptides, γ -aminobutyric acid and acetylcholine, may also modify hGH secretion.

However, most of these transmitters seem to act via somatostatin and growth hormone releasing factor rather than directly on the somatotroph cells (Reichlin 1992, Parks et al 1993, Wass and Besser 1995). hGH is shown to increase during exercise already at low intensities and reaches its maximal response at 70 % of maximal oxygen uptake (Galbo et al 1977, Luger et al 1992). The release of hGH is increased during slow wave sleep, particularly in the beginning of the night, and is inhibited by sleep deprivation (Parker et al 1979, Radomski et al 1992, Pietrowsky et al 1994). Growth hormone releasing hormone promotes sleep in animals (Kerkhofs et al 1993, Krueger and Obal 1993). Whether growth hormone has any sleep promoting effect in humans is, however, debated (Mendelson et al 1980, Kern et al 1993).

The dramatic increase seen in the plasma levels of growth hormone during the ranger course, is reversed in the subjects given a high calorie diet. In contrast, 3 hours of sleep each night during the course did not influence plasma levels of hGH. However, the plasma levels of hGH were increased if the blood samples were drawn just after the sleep period (Aakvaag et al 1978, Opstad and Aakvaag 1981, 1983, Opstad 1991). The absolute hGH response to the bicycle exercise test after an overnight fast was not increased above the enhanced pre-exercise levels during the course (Opstad et al 1980). The high calorie diet prevented the hGH increase during the exercise test during the course. In the control experiment the exercise test was performed after 8 -12 hours of fasting, whereas during the course the subjects of the high energy group could not be kept fasting for more than 4 hours before the exercise test. This shows that nutrients ingested in the hours preceding the exercise test may abolish the hGH response to an exercise test even during constant strenuous exercise.

Prolactin is one of the most versatile hormones, and its membrane receptors have a wide distribution to very different tissues such as mammary gland, liver, kidney, adrenals, ovaries, uterus, placenta, testis, prostate,

seminal vesicles, Leydig cells, hypothalamus, choroid plexus, pancreatic islets, lymphoid tissue, peripheral mononuclear cells, brain, intestine and others. Many tissues are known targets for PRL action, others are not.

Comparative studies indicate that osmoregulation and modulation of growth and development may be the most fundamental actions of prolactin. In humans, functions of PRL are still incompletely delineated but seem mainly to be involved in reproductive functions. PRL increases or maintains the concentration of LH receptors on the Leydig cell membrane, thus increasing the sensitivity of the testis to LH and by that enhancing plasma testosterone levels (Aragona et al 1977). PRL also potentiates the effects of androgens on the growth and secretory activity of male accessory glands and may even have direct androgenic effects. PRL in the seminal fluid also stimulates glucose and fructose utilization and the sperm motility and fertilizing capacity (for reviews see Reichlin 1992).

The pituitary secretion of PRL is under the control of hypothalamic release- and inhibiting factors such as the thyroid-releasing hormone, dopamine, glucocorticoids, oestrogen and epidermal growth factor. The circadian rhythm of PRL, with the highest levels in the early morning hours, may be due to the effect of both sleep and the circadian rhythm of melatonin (Spiegel et al 1994). This nocturnal increase is due to increased amplitude of the secretion pulses which have a frequency of approximately 14 per 24 h (Veldhuis and Johnson 1988). PRL has been shown to increase during different types of stress such as general anaesthesia (halotan), surgery, insulin-induced hypoglycemia and medication with a dopamine blocking effect, such as haloperidol or metoclopramid (Røjdmark and Rössner 1991, Wass and Besser 1995).

During the ranger training course there is a decrease in the plasma levels of PRL which may contribute to the decrease in testicular androgen secretion and which may also contribute to the hypoandrogenisation during the course by more direct ways. The relatively high levels of PRL before the start of the course may indicate that PRL is sensitive to the cadets' anxious anticipation before a strenuous course (Aakvaag et al 1978, Opstad and Aakvaag 1983, Voigt et al 1990, Opstad 1991, 1992). This is in spite of the fact that academic examination stress did not affect the plasma levels of PRL or hGH (Malarkey et al 1991). No alterations were found during the submaximal exercise test at 50 % of the cadets' maximal oxygen uptake before or during the course. In contrast, others have shown that exercise induces a rise in the plasma levels of PRL (Galbo et al 1977). The explanation is probably that, in contrast to the plasma levels of hGH which increase also at low exercise intensity, PRL increases only during high intensity exercise, which is 70 % of VO_2 max or more (Luger et al 1992). Since the exercise intensity during the course has a mean of approximately 35 % of VO_2 max, and the bicycle exercise test was 50 % of VO_2 max, this was below the intensity threshold for PRL release during exercise. It is, however, interesting to notice that even the strenuous physical activities during the course did not affect this threshold for PRL release. The small alterations found in the prolactin response to TRH during the course, might indicate that decreased plasma levels of PRL were due to dopamine inhibition, since dopamine is known to inhibit synthesis as well as secretion of PRL.

The adrenals, the gonades and the thyroid gland are regulated by the hypophyseal hormones ACTH, LH/FSH and TSH respectively. LH/FSH decreased during the course and is a main reason for the decreased plasma levels of gonadal androgens. The increased LH/FSH responses to GnRH stimulation during the course may indicate that the decreased gonadotropin levels are due to decreased hypothalamic secretion of GnRH although the decreased levels of androgenic hormones may also contribute to an increased LH/FSH response to GnRH stimulation. GnRH which is detected in septum, preoptic area, amygdala, and midbrain has its highest concentration in the median eminence, nucleus arcuatus, and organum vasculosum of the lamina terminalis. Secretion of GnRH is inhibited by dopamine and GABA and stimulated by α -adrenergic agonists, histamine and glutamate. Besides olfactory and visual inputs, GnRH secretion is also influenced by the pineal body and the nucleus suprahypophyseus. The feedback of gonadal steroids and inhibin both act at the hypothalamic secretion of GnRH and at the pituitary sensitivity to GnRH stimulation (Reichlin 1992, Hall and Crowley 1995, Lincoln 1995, Opstad 1990, Opstad et al 1994).

Thyroid hormones are mainly regulated by pituitary TSH which is stimulated by TRH produced in the paraventricular nucleus of the hypothalamus, inhibited by somatostatin produced approximately in the same area, the periventricular area, and by dopamine from the nucleus arcuatus. TRH is also influenced by the thermosensitive cells in the supraoptic nucleus, is stimulated by β -adrenergic agonists and may be inhibited by

serotonin. The negative feedback of thyroid hormones acts both at the hypothalamic and at the pituitary level (for review see Reichlin 1992, Scanlon and Hall 1995, Wondisford et al 1995)

The decreased TSH levels during the course would obviously contribute to the decreased thyroid secretion in spite of the fact that there was no direct connection between alterations in thyroid hormones and the decrease in TSH. The TSH response to TRH was reduced by 80 % during the course equally due to the strenuous physical exercise and energy deficiency, whereas sleep had minor significance (Opstad et al 1984).

Adrenal steroids are all stimulated by pituitary ACTH, which is under the control mainly of the hypothalamic CRH, but is also stimulated by AVP (vasopressin). CRH has also been localized to multiple brain areas, the spine and the gastrointestinal tract but with the highest concentration in the hypothalamus, particularly the paraventricular nucleus. The CRH neurones receive excitatory inputs from many brain areas such as nucleus suprachiasmaticus, amygdala and the raphe nuclei and inhibitory inputs from the hippocampus and the locus coeruleus. CRH secretion/release is stimulated both by acetylcholine, serotonin, and interleukin 1 and inhibited by GABA and nor-adrenaline. The negative feedback regulation by glucocorticoids may act at the pituitary as well as at the hypothalamic level, but there are also glucocorticoid receptors in various other parts of the brain such as in the amygdala and the hippocampus (for review see Reichlin 1992, Grossman 1995, Imura 1995).

The decreased ACTH levels measured during the training course could be due to the state of recovery just prior to the blood sampling since the subjects had only light physical activities 1-2 hours prior to blood sampling. The short half-life of ACTH compared to the long half-life for cortisol could explain the decreased ACTH levels during recovery (Opstad 1992a,b).

MENTAL PERFORMANCE AND CLINICAL SYMPTOMS

All mental performance and clinical symptoms have a biochemical or physiological basis, the disturbance of which will affect the soldiers' total performance. Sleep deprivation affects a series of mental functions, but does not affect the physical performance to any significant extent (Hill et al 1994, Reilly and Piercy 1994): First all subjective symptoms, such as the subjects' mood state, social well-being, ability to care for others, feeling of depression, and motivation will be affected. Then the most advanced mental performance tasks will be affected such as creativity, ability to solve complex mental performance tasks, or tasks requiring memorization and tactical abilities. With prolonged sleep deprivation the body's requirement for sleep increases so strongly that it becomes impossible to withstand sleep, and subjects will fall asleep even in the upright position. First, however, this will appear during the night-time, particularly in a period with rather low physical activities, in the form of extreme tiredness followed by balance disturbance, problems with straight walking along the roads, later with pseudo- or real illusions and hallucinations. In the beginning of the course the subjects take the hallucinations for real signs, whereas at the end of the course when they have got more used to them, they most often take all unexpected events as hallucinations. This might be a serious impairment of their function because they are not able to differentiate between real and not real signs and will be completely unfit for watchkeeping or surveillance tasks. These periods with intense feeling of sleepiness induce what has been called "microsleep" or lapses (Walter Reed Laps Hypothesis). The periods of microsleep increase in frequency and length almost proportionally to the length of sleep deprivation. The length might be from some seconds to several minutes and the frequency from some times a day to several times each hour, but still depending on the length of sleep deprivation and time of day (Johnson and Naitoh 1974, Opstad et al 1978, Haslam 1983, 1984, Angus et al 1987). During these periods the vigilance is so reduced that the subjects do not record even distinct signals in the environment. In the so called vigilance tests this gives error of omissions. In contrast, there are not many faults or wrong responses. The reaction time also increases and consequently all tasks therefore take more time than normal. On the third night of total sleep deprivation, the more serious signs appear, such as slow motions, balance disturbance, nystagmus, fog sight, disturbed distance vision, headache, visual hypnagogic hallucinations and physical exhaustion. In this state the soldiers are helpless and unable to manage their own situation. In stead of being a resource for the platoon, they become a problem. In such a state it is often observed that the cadets only disappear from the platoon or just sit/lay down and may fall into a state of sleep narcosis. They may be extremely hard to wake up. Due to

the internal sleep rhythm of approximately 90 minutes they may be much easier to wake up after only a few minutes. However, a sleep deprived person is possible to wake up for some seconds and then he will normally be oriented for time and site. This will make the difference to unconsciousness due to commotio cerebri which will be impossible to wake up by external stimulation.

Mental performance has a circadian rhythm with the highest performance in the afternoon and the lowest performance at night ($\pm 10-15\%$) (Bugge et al 1979, Czeisler et al 1980, Nickolson and Stone 1982, Folkard et al 1985). During the course there is a general decrease in mental performance; in addition the decrease is stronger during night-time than during day time leading to an increased amplitude of mental performance. This is not only due to the darkness of the night but also to endogenous circadian rhythms, since the same alterations are found in the courses organized in June, when the nights are rather light. All clinical symptoms are also more pronounced at night than at day-time. Almost all illusions, misperceptions, hallucinations, balance disturbances, and coordination problems are worse at night than during the day.

In contrast to the alterations in the circadian rhythm for mental performance which show increased amplitude during the course, the circadian rhythm of hormones are all extinguished during the course. The circadian rhythms are regulated from the nucleus suprachiasmaticus in the anterior hypothalamus (Van den Pol and Powley 1979, Rietveld 1992). This center is thought to regulate most of the known circadian rhythms. Previously it has been shown by Folkard (1985) that the period of the circadian rhythm for the feeling of alertness or drowsiness and deep body temperature dissociated when the period was shortened by 0.2 hours each day down to a "day" of 23 hours and then by 0.1 hour until a "day" of 22 hours which was run for the rest of the study. During the present military training course, it is shown for the first time that during continuous operations, a dissociation may appear between the amplitude of the circadian rhythm for mental performance which is increased, and the amplitude of circadian rhythm for steroid hormones which is extinguished. This indicates that these two rhythms are regulated by different mechanisms in the brain Opstad 1994.

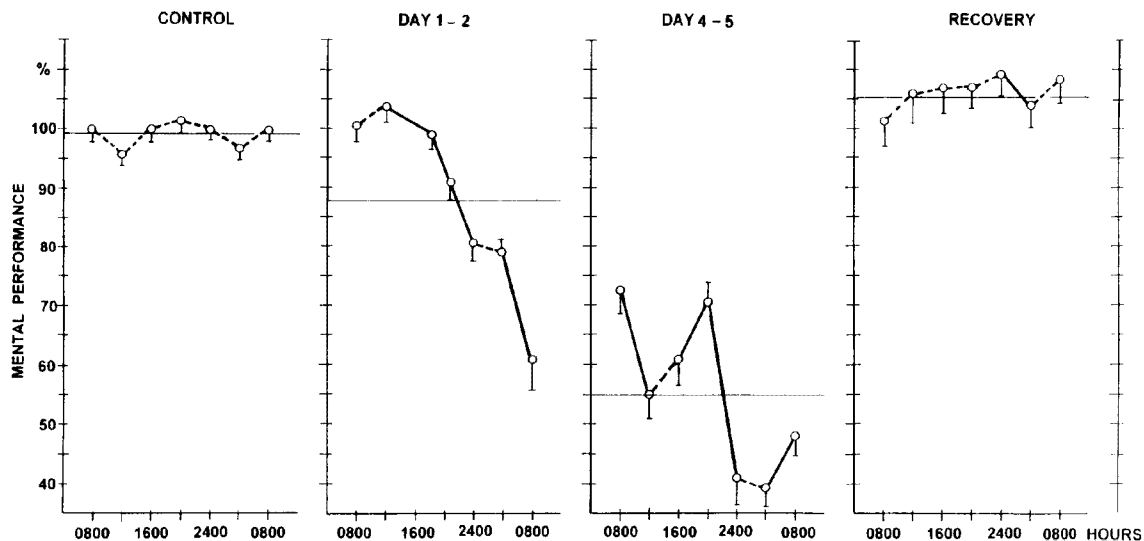


Fig. 11. The circadian rhythm for mental performance expressed as the mean of two mental performance tests; the code test and the logical reasoning test. The results are presented as per cent of the first test results (control at 08.00h) $\pm$ SEM. For details, see Fig. 8.

CONCLUSIONS

The present investigation shows rather large endocrine and metabolic alterations during a 5 day military training course with continuous physical activities combined with sleep and energy deficiency which might contribute to explain the accompanying alterations in both mental and physical performance. The main stress factors such as physical strain, lack of food and sleep all lead to an extreme catabolic metabolism with

similarities to the physiological state of the multitraumatized patients. One main finding is an adrenergic desensitization due to the physical strain, which is explained both by a decreased number and sensitivity of the adrenergic receptors and a decreased cAMP response to adrenaline stimulation. These alterations indicate that an important mechanism for reduced physical performance or exhaustion is target tissue desensitization.

The decreased levels of adrenal and testicular androgens and thyroid hormones may also contribute to alterations in both mental and physical performance. In addition the decreased thyroid hormones during the course may affect the cadets' cold tolerance. There is a dissociation between the circadian rhythm for mental performance, which is increased, and the circadian rhythms for steroid hormones, which are extinguished. This indicates that night activities are particularly strenuous and demanding for the cadets.

Some simple precautions or countermeasures, such as adjustment of the type and amount of food and sleep, may reduce the large impairment of the soldiers' mental and physical performance and prevent unnecessary health hazards.

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