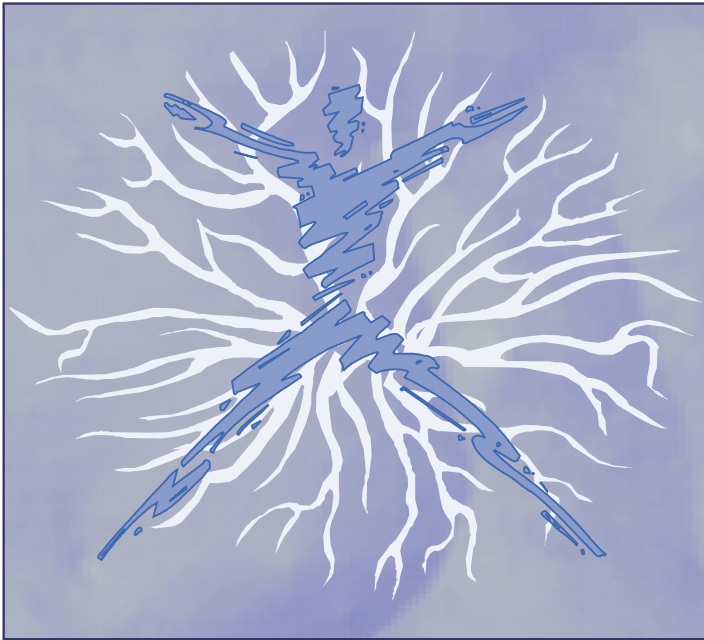


NUTRITION AND HEALTH COLLECTION

Stress and Nutrition: a Fascinating Crosstalk



*Danone Vitapole
Research*



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Stress and Nutrition: a Fascinating Crosstalk



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Abbreviations

AA: arachidonic acid
ACE: angiotensin-converting enzyme
ACTH: adreno-corticotropic hormone
AGRP: agouti related protein
AMPT: alpha-methyl-paratyrosine
AVP: arginine vasopressin
CART: cocaine and amphetamine regulated transcript
CHO: carbohydrate
CNS: central nervous system
CRF: corticotropin releasing factor
CRH: corticotropin-releasing hormone
CRH-BP: CRH-binding protein
CR-PP: carbohydrate-rich/protein-poor
DA: dopamine
GH: growth hormone
GnRH: gonadatropin-releasing hormone
GI: gastro-intestinal
HPA: hypothalamic pituitary adrenal
IBD: inflammatory bowel disease
IBS: irritable bowel syndrome
LAB: lactic acid bacteria
LC/NE: locus caeruleus/norepinephrine
LPS: lipopolysaccharide
LNAA: large neutral amino acids
MCH: melanin concentrating hormone
MDMA: methylene-dioxy-metamphetamine (ecstasy)
NA: noradrenaline
NE: norepinephrine
NK: natural killers
NPY: neuropeptide Y
OT: oxytocin
PMS: premenstrual syndrome
POMC: pro-opiomelanocortin
PDD: premenstrual dysphoric disorder
PUFA: polyunsaturated fatty acids
RDA: recommended daily allowances
RRS: revised restraint scale
5-HT: 5-hydroxytryptamin or serotonin
5-H-IAA: 5-hydroxy-indolacetic acid
TFEQ: three factor eating questionnaire
THC: tetrahydrocannabinol
TNF: tumor necrosis factor
TRH: thyrotropin-releasing hormone
TRP: tryptophan
UCN: urocortine
UCP: uncoupling protein

Introduction	9
1. Biological and physiological consequences of stress	10
Neuroendocrine and hormonal aspects	10
Effects on nutrition and the immune system.....	11
The gastro-intestinal tract and gut flora.....	13
2. Stress, eating, mood and behaviour	15
Neurotransmitters involved in food intake and pleasure	15
– <i>The tryptophan-serotonin system</i>	16
– <i>Other hypothalamic catecholamines</i>	16
– <i>Endogenous opioids</i>	17
– <i>The cannabinoid system</i>	18
– <i>Biochemical effects and the impact on mood of acute nutritional neurotransmitter depletion</i>	18
The place of food intake	19
Food craving, palatability and mood.....	21
Neurophysiological changes and membrane damage in subjects on a restricted diet.....	23
3. Major events, lifestyles, eating behaviour and stress	24
Emotions and eating behaviour.....	24
Dietary restraint.....	25
Premenstrual syndrome.....	26
Work and exercise	26
Vegetarianism.....	27

4. Stress, energy balance and body weight regulation	29
Energy balance	29
Body weight and weight loss	30
Obesity and body fat distribution.....	32
Exercise and changes in body weight	34
5. Stress and nutrition in pathological situations	35
Metabolism and body composition during starvation and malnutrition.....	35
Malnutrition, feeding behaviour and hospitalisation	37
Stress and inflammatory bowel disease.....	38
6. Some points on combatting stress	41
Oxytocin	41
Stress-relieving brain-food.....	42
– <i>L-tyrosine</i>	42
– <i>Serotonin-inducing diets</i>	42
Probiotics, and the immune and gastro-intestinal systems in exercise.....	44
Behaviour and cognitive involvement	45
Chocolate, an “anti-stress food”?.....	45
Conclusion	47

INTRODUCTION

Stress is a diverse, complex phenomenon with many components between the triggering event, through processing in the brain, to the response. The responses – which may be emotional, biological or physical – varies enormously from individual to individual because of both genetic and environmental factors, but it often affects eating behaviour. The stress response is an adaptive mechanism. In most cases, the adaptation is physiologically appropriate and so has to be maintained, but in others it can have pathological consequences.

Stress is very difficult to define: in 1936, Selye proposed a model in which stress is seen as a cascade with a triggering event, a compensatory reaction and then the establishment of a new, homeostatic balance. In common parlance, the word stress is used to refer to the triggering event itself or the reaction it elicits. There is a tendency to identify triggering factors as situational (*e.g.* loneliness or tiredness), biological (premenstrual syndrome, seasonal depression, etc.) or self-induced (nicotine withdrawal, dieting, etc.), rather than as biological effects of endocrine factors on the immune system, the gastro-intestinal tract, metabolic function, behaviour or mood.

Eating behaviour is the most effective outlet for modulating the consequences of stress (*e.g.* hypophagia or a craving for carbohydrates), but it can also create and modulate stress (*e.g.* in dieters).

Although it is almost impossible to be exhaustive on the subject, this booklet will give an interesting overview of this very important topic.

BIOLOGICAL AND PHYSIOLOGICAL CONSEQUENCES OF STRESS

NEUROENDOCRINE AND HORMONAL ASPECTS

The hypothalamic-pituitary-adrenal (HPA)-axis acting together with the sympathetic nervous system mediates the peripheral effects of centrally perceived stress: the central nervous system (CNS) centres of the HPA-axis are the parvocellular corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) neurons of the paraventricular nuclei of the hypothalamus; and those of the sympathetic nervous system are the noradrenergic neurons of the locus caeruleus/noradrenaline (LC/NE) nuclei of the brain stem. These centres are connected to one another and interact extensively. Both these systems have a baseline circadian rhythm and are active during stress. Activation of the stress system leads to behavioural and peripheral changes that enhance the body's ability to adapt and increase its chance of survival.

The CRH/AVP neurons are interconnected with the noradrenergic neurons of the LC/NE system in a positive feedback circuit. Activation of the HPA-axis by stress-induced CRH and glucocorticoids inhibits the secretion of gonadotropin-releasing hormone (GnRH). At the same time, somatostatin is inhibiting the secretion of growth hormone (GH/IGF1), thyrotropin-releasing hormone (TRH) and thyrotropin; finally, sympathetic activation increases IL-6 secretion.

Furthermore, glucocorticoids modulate the antagonistic effects of neuropeptide Y (NPY) and leptin which are responsible for maintaining normal body weight. Adrenalectomy is known to prevent some types of obesity. Stress-induced glucocorticoids could increase NPY levels and counter leptin activity.

CRH is considered as the most important releasing hormone in adrenal activation, whereas arginine vasopressin (AVP) is considered as the main ACTH-releasing factor in neurogenic stress. In humans, psychogenic stress induces an AVP-specific neurophysin and stimulates ACTH and cortisol production without any effect on CRH levels.

In rats and humans, oxytocin (OT, the structure differs from that of AVP at only two residues) has an antagonistic effect to that of AVP on memory. It has been demonstrated that OT induces a reproducible, dose-dependent decrease in ACTH (thereby antagonising the effect of AVP) and inhibits the adrenal gland. Thus, this inhibitory effect is secondary to a central pituitary effect and peripheral inhibition of steroidogenesis.

Therefore, OT and AVP have antagonistic effects on adrenal activation during metabolic stress. Since AVP is also implicated in adrenal activation as an important co-factor for CRH during neurogenic (psychological) stress, it is likely that centrally released OT (from the median eminence) acts to buffer the various metabolic and behavioural effects of AVP and adrenal activation.

The overall action of AVP would seem to be directed towards maintaining homeostasis in the individual (water retention, high blood pressure, increased memory, etc.) whereas that of OT tends to promote the well-being of the group (*e.g.* the family or the species). Apart from its clinical role in foetal expulsion, the anti-stress effect of OT could be particularly useful in mothers – when the baby cries, more milk is produced!

EFFECTS ON NUTRITION AND THE IMMUNE SYSTEM

The immune system is based on both antigen-specific mechanisms (*i.e.* the humoral system which produces antibodies and the cell-mediated arm) and non-specific defence mechanisms like the barrier function of skin and mucus, phagocytes, the complement pathway, lysozyme, cytokines, etc. Cytokines are biologically active polypeptides which are released from activated cells (often lymphoid cells). They have many different effects but all tend to induce metabolic changes following stress or aggression. They stimulate the peripheral release of energetic substrates (glycogen and amino-acids from muscle and lipids from adipose tissue) for metabolism in the liver and other vital organs. These substrates provide essential molecules (especially nitrogen) for the construction of tissue and for the synthesis of inflammatory proteins.

In recent years, it has been observed that stressed animals are more susceptible to certain types of disease like infection (*e.g.* colds and influenza) and cancer. In humans, a healthy lifestyle is associated with elevated NK cell activity. Recent data have shown that obesity may be due to stress-mediated activation of the HPA-axis with concomitant changes in immune function as detected by elevated numbers of leukocytes and of certain subsets of lymphocytes (not including NK cells and cytotoxic/suppressor T cells), suppressed mitogen-induced lymphocyte proliferation (which measures T and B cell function), and increased phagocytic and oxidative burst activity in monocytes and granulocytes.

Leptin, the appetite-regulating hormone, has a cytokine-like structure (as does GH) and seems to act as a powerful stimulator of one part of the immune system. Leptin has a complex relation to the HPA-axis, possibly stimulatory at some level but also presumably antagonising cortisol. Cortisol down-regulates cytokines like IL-1, IL-6 and TNF- α , which all activate the HPA-axis (*figure 1*): IL-1 can inhibit insulin production; TNF causes insulin resistance; and IL-6 stimulates lipolysis and raises blood glucose levels. IL-1 can cause malaise and may induce – together with TNF- α and IL-6 – fever and tiredness as well as stimulate the release of leptin (which is the main reason why people loose their appetite during an infection). Haematopoietic cells express leptin receptors which are stimulated in the foetus and in adults. Leptin prevents apoptosis of lymphocytes in the thymus and selectively stimulates Th₁ lymphocytes (although resistance to leptin is seen in obese subjects). It has been shown recently that high concentrations of leptin stimulate the differentiation of CD34+ myeloid progenitor cells from human bone marrow and this may be involved in the leukocytosis commonly observed in obese subjects.

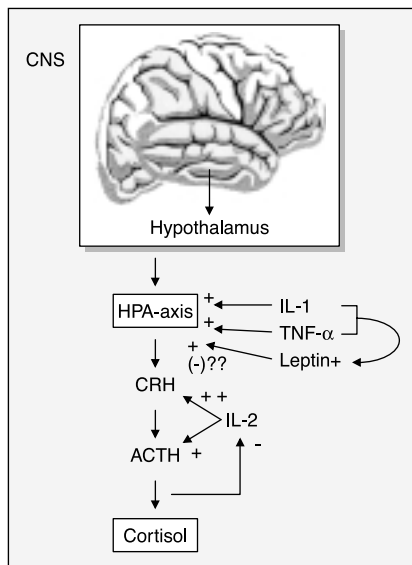


Figure 1. The HPA-axis and cytokines-leptin (reproduced from Hanson).

The effect of stress on immune function may be due to the wide range of secondary effects resulting from high plasma glucocorticoid concentrations, especially corticosterone which is rapidly induced by stress. Possible effects include lymphocytopenia, thymus involution, and the loss of tissue mass in the spleen and peripheral nodes. The stress system is known to inhibit inflammatory and immune responses. It does this by modifying leukocyte migration and function, and by modulating the effects of inflammatory mediators: not only is the production of such mediators inhibited, but the stress system also decreases the responsiveness of the target tissues (*e.g.* the gastro-intestinal tract).

Stress and nutrition have a synergistic effect on the immune system. The impact depends on the individual's nutritional status, on the nature and the duration of the stress

(such as infection, etc.), and on the subject's diet during the recovery period. Almost any kind of nutrient deficiency will compromise the immune functions and capacity to defend the organism against exogenous insults: this can pertain even when the deficiency is relatively mild, particularly when it comes to iron and protein-energy malnutrition, but also with respect to selenium, zinc, and vitamins A, C, E, B6 and B9 which are all required for immune responses. Impairment may affect both humoral and cell-mediated mechanisms with reduced immunoglobulin concentrations, decreased numbers of thymic and splenic lymphocytes, reduced complement production, reduced immunoglobulin A and interferon secretion, fewer T cells in general and lower numbers of certain T cell subsets in particular, as well as decreased expression of interleukin-2 receptors.

THE GASTRO-INTESTINAL TRACT AND GUT FLORA

The gastro-intestinal tract has a surface area of some 400 m². It accounts for two-thirds of the body's immune system and contains as much nervous tissue as the spinal cord. The intestinal mucosae contain all types of immunocompetent cells as well as polymorphonuclear leukocytes. A very large proportion of all the body's lymphocytes are found in the intestine and its lamina propria contains the highest density of plasma cells in the body. Immunocompetent cells are distributed throughout the epithelia of the intestine and the colon, often forming aggregates like those in the appendix vermiformis and Peyer's patches. Humoral mucosal immunity largely corresponds to the secretory immunoglobulin IgA which is produced by plasma cells. This immunoglobulin is particularly important in inhibiting the adhesion of bacteria to the intestinal epithelium and also plays a role in neutralising viruses and sequestering antigens. The beneficial effects of breast milk are largely due to the fact that it contains high levels of IgA antibodies (*figure 2*).

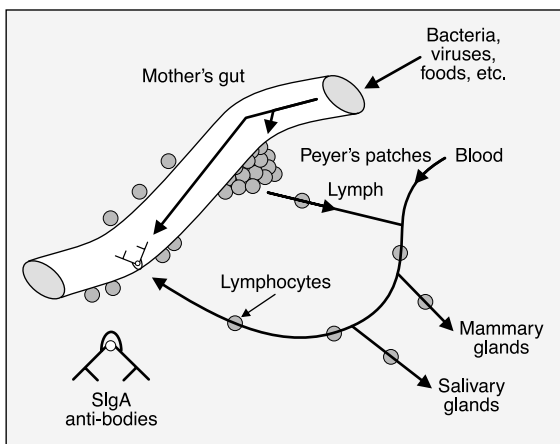


Figure 2. Breastfeeding protects especially via secretory IgA antibodies (reproduced from Hanson).

The gastro-intestinal tract, and especially the intestine, contains at least 10 times more bacteria than there are eukaryotic cells in the body (about 10^{13}). In new-born babies, the number of anaerobic bacteria increases slowly after birth, whereas aerobic bacteria colonise more rapidly (10^{10-11} bacteria per gram of feces). In adults, anaerobes account for over 99% of the intestinal flora and prevent the growth of other types of bacteria (one gram of adult feces only contains 10^{6-9} aerobic bacteria).

Certain cytokines have potent pro-inflammatory and metabolism-modulating activities and some of these key immune modulators are directly induced by common intestinal bacteria. For example, bacteria can stimulate leukocytes to produce both IL-10 and IL-12 which selectively stimulate different components of the immune system (with ultimately antagonistic effects) and profoundly affect metabolic function. When the normal balance of the intestinal flora is disturbed, the body may experience physiological and pathogenic effects. Changes in floral composition occur naturally during ageing, eating and breast-feeding, or in response to diverse environmental factors, but psychological stress (in the form of repeated, mild but unpredictable insults in rats) is also known to affect the bacterial profile in feces with an increase in the numbers of vegetative organisms and *Clostridium perfringens* spores. In some cases, this is associated with neuroendocrine and metabolic disturbances.

STRESS, EATING, MOOD AND BEHAVIOUR

There is a great deal of clinical and anecdotal evidence to suggest that there is a link between certain stressful situations and eating behaviour. Such situations include self-induced events like quitting smoking and dieting as well as physiological and pathological states like premenstrual syndrome and seasonal depression. As everybody knows, when eating is used for its effect on mood, it tends to be carbohydrate-rich, high-fat food-stuffs which are consumed rather than less palatable foods.

Experimental studies in animals show that the response depends on the nature of the stress and the dietary environment. For example, if the stress is mild (*e.g.* pinching the tails of rats, an annoying but painless insult) and food is present, there is a period of hyperphagia. In the case of cafeteria diet, body weight increases rapidly. In many cases, once the stress is removed, there is a period of hypophagia until normal body weight is re-established.

More intense stressful stimuli (*e.g.* high temperature) induce a period of anorexia which is not compensated with increased food intake when the stress is lifted.

NEUROTRANSMITTERS INVOLVED IN FOOD INTAKE AND PLEASURE

The following section deals with how the wish to mitigate discomfort, pain or any other kind of adverse event may be linked with food intake and the pleasure to be derived from eating.

Many different neurotransmitters in the brain are involved in the central regulation of food intake and the systems that they constitute are linked to both homeostatic mechanisms and emotional processes:

- the tryptophan (TRP)-serotonin (5-hydroxytryptamin or 5-HT) system,
- catecholamines and other hypothalamic monoamines (noradrenaline and dopamine),
- endogenous opioid peptides,
- the cannabinoid system.

The tryptophan-serotonin system

Serotonin (5-HT) is synthesised from the dietary amino-acid tryptophan (TRP), and brain 5-HT concentrations rise when TRP is directly administered or when the diet is rich in carbohydrate (CHO) and poor in protein (a CR-PP diet). The plasma TRP concentration is high compared with that of all the other large neutral amino acids (the TRP-LNAA ratio) and a greater proportion of TRP is transported into the brain (because the transport system is a competitive one). An increase in the plasma TRP-LNAA ratio on a CR-PP diet is caused by the CHO-induced rise in glucose levels which triggers insulin secretion and promotes LNAA transport (other than that of TRP into skeletal muscle tissue). A protein-rich diet decreases the plasma TRP-LNAA ratio because proteins contain relatively little TRP (1-2%) but large quantities of the other LNAAs, valine, tyrosine, leucine, isoleucine and phenylalanine (25%). These effects of diet on the plasma TRP-LNAA ratio have been extensively documented.

Enhanced brain 5-HT activity is a well-demonstrated consequence of stress whereas inhibition of central function has been shown in mood disorders like depression, seasonal depression or premenstrual syndrome. Hence, increases in 5-HT may enhance the capacity to respond to stress and prevent further degeneration in terms of mood.

Several studies have investigated the effect of diet-induced changes in plasma TRP-LNAA ratios on mood. For example, a CR-PP diet inhibits depression and enhances cognitive performance in stress-prone subjects (but not in more stress-resistant subjects) under uncontrollable experimental stress conditions (*figure 3*).

Other hypothalamic catecholamines

Dopamine (DA) has been shown to be one of the most important appetite-related neurotransmitters in the brain. DA-deficient knockout mice (which express no tyrosine hydroxylase) could not initiate feeding and this deficiency could be corrected by delivering a functional copy of the missing gene into the corpus striatum. Thus, it has been proposed that DA is required to initiate each meal, and it can therefore be linked with meal frequency, at least with respect to its action in the forebrain. Increases in DA levels in the medial hypothalamus – the area responsible for the neuroendocrine and autonomic regulation of metabolism – have been observed following the intake of food.

Tyrosine is a precursor of noradrenaline (NA) and enhances the synthesis of this important neurotransmitter. Noradrenergic activity in the frontal cortex plays an important

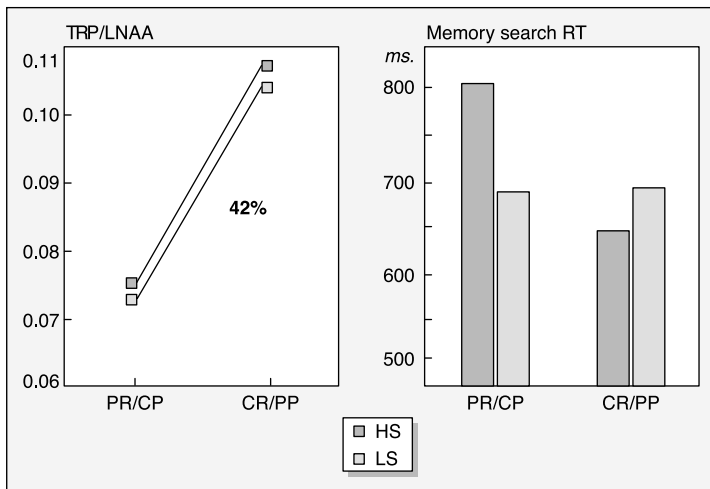


Figure 3. Carbohydrate-rich, protein-poor diet improves memory search time in 43 young healthy stress prone subjects (reproduced from Markus *et al. Br J Nutr* 1999; 82: 457-67). HS = High Stress-Proneness; LS = Low Stress-Proneness; RT = Reaction Time.

role in attention, alertness, emotional processes and motor activity. In the frontal cortex, stressful events induce increased transmission in noradrenergic neurons. Activity in a set of noradrenergic projections from the locus caeruleus (which provide the main connection to the frontal cortex) is increased in times of stress. Stress and fatigue-induced depletion of brain NA is associated with behavioural depression in animals, and inhibiting NA release in humans causes attentional lapses. Psychosocial and physical stress increase the rate of release of NA in both the periphery and the central nervous system. In rats being fed a tyrosine-rich diet, no NA depletion or behavioural impairment was observed in response to stress. Humans exposed to cold and hypoxia had fewer symptoms of stress when they were eating a diet supplemented with tyrosine, and they also showed better psychomotor and 5-HT-memory performance. Protein-rich diets increase brain and plasma tyrosine levels. So tyrosine supplementation may be able to prevent stress and fatigue due to NA depletion. Such a diet should also preserve cognitive function.

Endogenous opioids

Endogenous opioid peptides are involved in the regulation of calorie intake in humans. Several studies have shown that the opioid antagonists, naloxone and naltrexone, reduced the intake of laboratory chow in both rats and mice. When selective antagonists of μ , κ and δ receptors were administered centrally, similar reductions in food intake were observed. Conversely, in rats, the administration of both opioid agonists (morphine and butorphanol) and agonists of specific opioid receptors (μ , κ and δ) had the reverse effect and stimulated food intake.

In clinical studies, the opioid antagonist naloxone reduced food consumption in both normal and obese subjects, and it also cut down the amount of food consumed by

female bulimics in the course of “binges”. Similarly, naltrexone appeared to reduce the amount of food consumed by obese subjects. Conversely, food intake was increased by the opioid agonist bupropion.

Opioid peptides seem to have a greater effect on the consumption of the most palatable foods. Animal experiments that studied the effects of opioid antagonists on different diets found that naloxone and naltrexone caused greater reductions in the intake of palatable foodstuffs than of standard laboratory chow.

Other studies addressed the effects of opioid peptides on the consumption of two palatable dietary ingredients – fat and sugar. Naloxone suppresses stress-induced sucrose hyperphagia and selectively reduced intakes of CHO and fat when subjects were free to choose their own diet. Conversely, the agonists morphine and bupropion selectively increased fat consumption. Some investigators have proposed that the primary role of the opioid system is to promote consumption when palatable or high fat foods are available. Opioid peptides may thus influence calorie intake by mediating the pleasure response to food. Sensory preferences for sweet foodstuffs in particular appear to be under opioid control. It may be that blocking the opioid pathway renders palatable food less rewarding.

Thus opioids are important in the short term control of food intake and modulate the pleasure response to alimentary stimuli: agonists enhance the response and antagonists attenuate it. Such an action corresponds to a control of food palatability or, in humans, to a control of the sensory pleasure and displeasure associated with food stimuli. The opioid system does not seem to act directly on body weight regulation.

The cannabinoid system

The active compound of cannabis, Δ^9 -tetrahydrocannabinol (THC), is known to bind to a specific receptor which is concentrated in one part of the cortex and in the hippocampus and corpus striatum, *i.e.* areas involved in psychological, behavioural and cognitive function. The natural, endogenous ligand for this receptor in the brain has been identified as anandamide (N-arachidonoyl ethanolamine) which is a derivative of arachidonic acid (AA). Other anandamines derived from other fatty acids (*e.g.* dihomo- γ -linolenic acid, the precursor of AA and adrenic acid derived from AA) have been isolated.

Increased amounts of another, more recently discovered, cannabinoid compound – 2-arachidonoyl-glycerol – are released from nerves which contain glutamate, a neurotransmitter involved in memory. Cannabinoid receptor agonists increase appetite, whereas antagonists reduce food intake, perhaps because of interactions with dopamine which stimulates anandamide synthesis.

Biochemical effects and the impact on mood of acute nutritional neurotransmitter depletion

The major serotonergic and dopaminergic pathways are found in the brain where they are intimately interconnected.

A lack of indoleamine or catecholamines has been linked to depressions. Anti-depressant drugs act by inhibiting the re-uptake or breakdown of 5-HT or NA.

Neurotransmitter depletion can be induced by administering a formula which is rich in the other amino acids but does not contain any TRP. TRP deficiency leads to 5-HT depletion (scores on the Hamilton Depression Scale associated with this kind of deficiency showed gender-dependent differences). In depressed patients, there is a threshold effect with no further change in mood after depletion of either TRP or AMPT. In volunteers, TRP depletion exacerbated depressive symptoms in 80% of all subjects with a more marked effect and a higher likelihood of relapse in females. There was a strong association between the SLC6A4 genotype and a depressive response to TRP depletion.

THE PLACE OF FOOD INTAKE

We have seen which neurotransmitters are involved in food intake and how they are to some extent associated with effects on mood (pleasure, etc.) and behaviour.

Both human and animal studies on stress and eating reveal that stress can lead to an increase and decrease in food intake.

Stress-induced effects on eating and food choice are observed in various circumstances: stress-coping strategies (e.g. eat for distraction and emotional eating); motivation-related consequences (e.g. reduced concern about weight control and a feeling of helplessness); physiological effects on appetite due to stimulation or cachexia; practical changes in eating opportunities and the availability of food.

Possible predictors of susceptibility to stress-induced eating include the nature of the stressor (its severity, whether it is emotional or physical, work-related stress), the subject's predisposition to and ability to cope with stress (physiological and psychological reactivity), individual differences in eating behaviour (dieting, emotional eating, gender-dependent food preferences, nutritional status), and the palatability and availability of the food.

At times of stress, there is some evidence that more snacks and higher levels of fat are consumed. In a subjective study on stress-related eating in students, a consistent pattern in food choice was observed: sweets and chocolate were always consumed in quantity, while meat and fish were avoided in all participants, irrespective of the subjects' own assessments of their predisposition to stress-induced eating. Moreover, stress induced a wide range of different effects with a large proportion of the women (40%) eating more, but an equal fraction of men (40%) eating less or even much less (*figure 4*). However, about 70% of all subjects reported eating more snacks (including many of those who ate less overall in times of stress), although 10% reported snacking less often (*figure 5*).

In a laboratory study, stress was induced by instructing the subjects that they were to give a public speech immediately after lunch with ten minutes preparation time before lunch – this meant that the stress was sustained during eating. Food was provided *ad libitum* (in the form of a varied, cold buffet) and the foods chosen by subjects of the

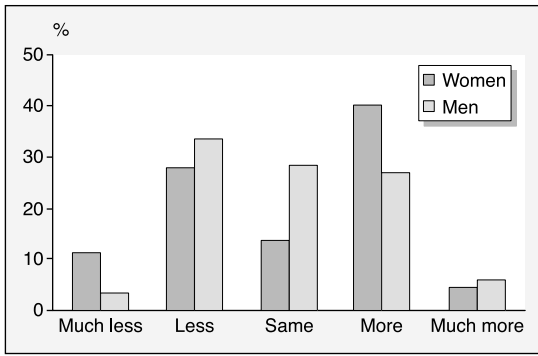


Figure 4. Reported change in amount of food eaten under stress (reproduced from Oliver and Wardle, 1999).

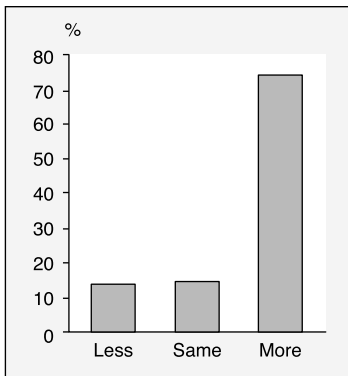


Figure 5. Change in snacking under stress (reproduced from Oliver and Wardle, 1999).

stressed group were recorded and compared with those chosen by a control group given a non-stressful task to perform. Total intake was similar in both groups but, in the stressed group, emotional eaters tended to choose sweeter, higher-fat foodstuffs than the others (figure 6).

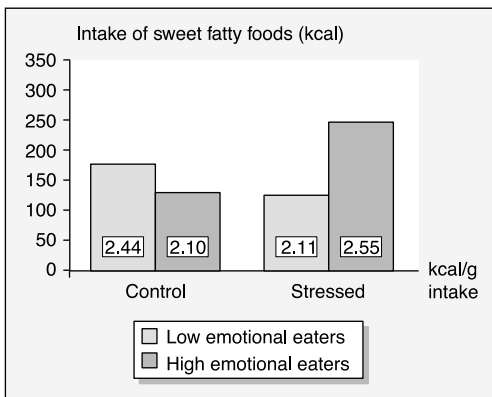


Figure 6. Stress increases intake of sweet fatty foods in emotional eaters (reproduced from Oliver, Wardle and Gibson, 2000).

FOOD CRAVING, PALATABILITY AND MOOD

Stress is not simply a response but an imbalance between demands and coping resources. Carbohydrate craving and certain mood disorders like dysphoria in depression, seasonal affective disorder or premenstrual syndrome may be indicative of the existence of some form of stress. Although the relationship between food craving (mainly carbohydrate craving) and mood has received considerable scientific attention in recent years, there has been little direct focus on the impact of stress.

Food craving is often defined as an intense desire for a particular foodstuff or type of food. Food cravings are quite common. Numerous potential aetiological factors have been proposed, including food deprivation in both normal and obese people on low-calorie diets. It has also been suggested that certain foods are craved because they contain neurochemically active substances which induce a feeling of well-being.

An influential hypothesis proposes that carbohydrate produces a transient feeling of well-being by raising the level of serotonin in the brain. There are a number of reports that carbohydrate (CHO) intake is associated with mood enhancement: among obese women, a high CHO intake, particularly that of simple CHOs, is consistently associated with lower levels of both anxiety and depression; and in the general population, experiments based on both *ad libitum* eating and specially designed meals have shown that a carbohydrate-rich diet is associated with improved mood.

In highly stressed subjects (with both controllable and uncontrollable stress), a carbohydrate-rich/protein-poor (CR-PP) diet attenuated depression and resulted in sustained levels of cortisol and vigour.

Investigations into the physiological link between dysphoria and CHO craving have generated much apparently contradictory evidence. There is good evidence that a meal almost exclusively made up of CHO increases the availability of tryptophan (TRP) in the blood and its rate of entry into the brain, thereby enhancing serotonergic neurotransmission. However, there is no evidence of any increase in serotonin (5-HT) release even when the levels of TRP have been shown to have risen. Following the intake of pure CHO, TRP levels only begin to increase after two to three hours but mood enhancement is observed within one hour, *i.e.* before 5-HT synthesis has been up-regulated – the timing is all wrong. It has also been proposed that as little as 2-5% protein in a high CHO meal can prevent the increase in availability of TRP. This might explain why, despite high TRP intake, a high protein/low CHO diet is associated with anxiety in normal (*i.e.* without any psychiatric problems), obese women.

Examination of the effects of CHO reveals that there is a complex relationship between CHO consumption and emotional distress, and that individuals with depressive symptoms show a preference for sweet-tasting, simple CHO. This does not necessarily imply a direct physiological relationship but may rather be associated with palatability. Sweetness is innately attractive and is particularly attractive when combined with high fat

content. So, do only pleasant tasting foods improve mood? Is the choice of such foodstuffs due to sensory gratification?

It is known that eating palatable foods induces the release of endorphins, the endogenous opioids. In rats and in humans, morphine increases food intake whereas opioid receptor antagonists tend to decrease the intake of palatable food (CHO and fat) to a greater extent than that of normal food. It has been demonstrated experimentally that higher CHO intake is associated with better mood in men but not in women (the presence of fat in the food does not change this picture) and fasting is associated with depressed mood. However, the change in mood is not associated with glucose levels or related to the intake of macronutrients after a specially designed breakfast containing 50 grams of available CHO (although subjects with a high blood glucose level did report better mood). Late in the morning, the mood of subjects who had a snack was more depressed than those who had no snack, whatever or not they had had breakfast. Attempts to investigate the effect of the macronutrient content of breakfast have found that the rate at which the meal is eaten is more important than its nature.

Much research has focused on the hypothesis that (CHO) cravings are produced by physiological imbalance, but there is much evidence of the contrary. The most frequently self-reported motivation for cravings is sensory gratification. There are many reports suggesting that, at times of emotional distress, the intake of palatable foods (those containing high levels of both fat and CHO) increases. This highlights the importance of palatability and, perhaps, of endorphin release. Both drugs and palatable foods are rewarding even when the organism is not in a state of need.

Conditioning is an important possible factor to explain stress-related food craving. Cues that accompany food intake (including stress) may start to act as conditioned stimuli which trigger a pre-programmed response.

In this process, a conditioned stimulus previously associated with some specific type of food produces thoughts of that food which leads to behaviour aimed at obtaining and consuming it. This conditioned response could be abolished if the stimulus is repeatedly presented without the food being eaten. Being distracted can also contribute to explaining the relationship between stress and compulsive eating (in a diversionary strategy), in order to attenuate negative feelings; thus the objective of eating and/or having a food craving is not only to alleviate the stress but also to avoid the feelings. Distraction could be a factor which leads to conditioned responses becoming important in the relationship between stress and eating behaviour.

Hence, future explanations of the relationship between stress and food cravings will involve palatability, distraction and conditioning. Any model should integrate all these factors together with individual differences (both psychological and physiological) within a conditioning framework.

NEUROPHYSIOLOGICAL CHANGES AND MEMBRANE DAMAGE IN SUBJECTS ON A RESTRICTED DIET

Neurochemical changes have been proposed as being important factors in the aetiology of depression in subjects on a restricted diet because it is known that a number of neuroregulators, including neuropeptide Y (NPY), the opioids and serotonin, can be directly influenced by diet.

NPY modulates numerous brain functions, including endocrine, behavioural and circadian processes. Recent studies have indicated that a reduction in the level of NPY in the central nervous system may play a role in depression. There is also evidence that denial of food affects NPY gene expression and the level of the peptide in the paraventricular nucleus of the brain in animals with a caloric deficit. In these cases, not only are endogenous opioid levels reduced, but also that there is less opioid binding in several areas of the brain, most notably in the amygdala, the control centre for emotion. So dieting-induced suppression of opioid activity may contribute to psychological distress because the opioids mediate the pleasure response to eating.

Several studies have demonstrated that dieting reduces both total plasma tryptophan and the ratio of tryptophan to large neutral amino acids in the plasma. Monkeys which had been fed a low-fat diet were observed to produce less oxytocin in response to a fenfluramine challenge. On a low-cholesterol diet, monkeys were shown to have lower levels of the serotonin metabolite 5-hydroxy-indolacetic acid (5-H-IAA). Serotonergic changes are a well characterised feature of depression.

Apart from the pronounced neurochemical changes observed in subjects on a restricted diet, it is possible that the diet may induce physiological changes in the lipid composition of neuronal membranes, *e.g.* depletion of total membrane fatty acids or preferential utilisation and excretion of ω -3 fatty acids. Inadequate dietary ω -3 fatty acid intake had a noticeable effect on monoaminergic transmission in the frontal cortex of rats and resulted in an increase in the density of serotonin 2A receptors in the frontal cortex and a simultaneous decrease with respect to D₂ receptors. A similar pattern has been observed in the frontal cortex of suicide victims. It has also been shown that a diet deficient in ω -3 fatty acids inhibits the release of melatonin which is involved in the sleep/wake cycle and seasonal depression. Melatonin levels can be restored by supplementation of ω -3 rich phospholipids. Hence, dopaminergic and serotonergic function seems to be influenced by the fatty acid composition of cells in the frontal cortex, and ω -3 fatty acid deficiency could be a factor contributing to catecholaminergic disturbance in depression.

Reduced serotonin levels, neurochemical imbalances, changes in membrane PUFA concentrations, and the anxiety which is associated with tolerating and sticking to a restricted diet – all these factors may contribute to depression in dieters.

It would be premature to assume that reduced energy intake is the only consequence of a restricted diet.

MAJOR EVENTS, LIFESTYLES, EATING BEHAVIOUR AND STRESS

EMOTIONS AND EATING BEHAVIOUR

Emotions affect a number of processes related to eating, including the motivation to eat, food choice, hedonistic responses to food, food frequency and the overall amount of food ingested.

Emotional eating can be defined as a change in eating behaviour which is induced by an emotion or the individual's anticipation of an emotion and which is designed to change or regulate this emotion (whether intentionally or unintentionally). Emotional eating covers a wide range of different phenomena, including fast eating in rats exposed to environmental stressors, disinhibited eating in normally restrained eaters in times of emotional upset, and loss of appetite in depression. Research has tended to focus on the role of individual characteristics in emotional eating while neglecting the role of emotions. However, it seems reasonable to assume that the particularities of the emotions involved will also play a major role in their effects on eating behaviour. For example, an emotion like fear, which is mainly characterised by behavioural inhibition, will be less likely to trigger an eating response than emotions like anger or distress which tend to stimulate action.

Some recent studies have demonstrated that different emotions have different effects on appetite in normal subjects. In a study based on answers to a questionnaire on the triggers for impulsive (binge) and sensory eating, anger was rated higher than either sadness or fear (which were equivalent). For hedonistic eating, joy scored the highest. In a field study, subjects were asked to assess their emotional state and their motivation to eat for a period of six days. Cluster analysis showed that certain reasons for eating were rated higher during times of negative emotion than during times of positive emotion. These reasons were to relax, to provide distraction, to feel better. No differences were recorded

between the various positive emotional states, *i.e.* a relaxed state, joy, or no particular emotion. Subjects also reported feeling more hungry during negative emotional states.

DIETARY RESTRAINT

Dietary restraint is largely, if not predominantly, a psychological issue. It is a struggle between a physiologic need or want, and a desire to lose weight or a fear of gaining weight. Recent studies have shown that many dieters are not restrained eaters and that only a small percentage of restrained eaters are dieting at any given point in time.

According to subjective surveys, both restrained eaters and those on a diet at the time are more likely to overeat in response to stress. Restrained eaters, bulimics and binge eaters tend to increase their food intake in response to negative emotions. Several laboratory-based studies have compared the effects of a stressor on eating in low and high restrained eaters. The findings have been quite consistent in that, when stressed, restrained eaters tend to eat more, whereas unrestrained eaters eat less (*figure 7*). However, in these studies, the food was presented in a deliberately fortuitous manner and typically made up of small snacks. When the effect of stress (in the form of anticipated public speaking) on eating at midday was investigated, total intake was unaffected by restraint or stress but those with a tendency to emotional eating ate more sweet and high-fat food.

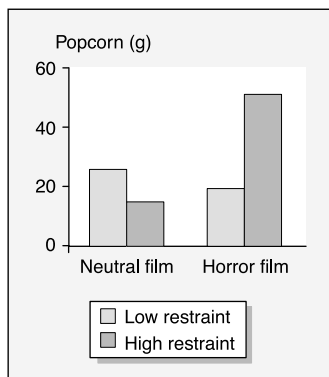


Figure 7. Intake of snack foods under stress (reproduced from Cool *et al.*, *J Abnorm Psychol* 1992; 101: 348-51).

Some restrained eaters will overeat (disinhibition) in response to a stressor which has elicited negative affect. Disinhibitors can be cognitive, emotional or pharmacological. However, this only appears to be the case when restraint is measured on the Revised Restraint Scale (RRS). The relationship between restraint (subjects were classified as either high restraint or low restraint) or disinhibition (high disinhibition or low disinhibition) as measured by the Three Factor Eating Questionnaire (TFEQ) and food intake in response to a stressor was investigated in 80 females. The most acutely disturbed eating patterns were observed in highly restrained, highly disinhibited individuals who were significantly more likely to report episodic overeating, binge eating or binge eating syndrome. Comparison of overall food intake indicated that, in response to stress, those in the low restraint-low

disinhibition group increased their food intake (contrary to predictions made by restraint theory) whereas those in the high restraint-high disinhibition group ate less. So the effects of negative affect on eating behaviour vary as a function of both restraint and disinhibition which interact with one another.

PREMENSTRUAL SYNDROME

Premenstrual syndrome (PMS) is characterised by a number of emotional and physiological symptoms that occur during the last part of the luteal phase of the menstrual cycle. The most severe form of PMS is listed as premenstrual dysphoric disorder (PDD). At least 75% of women experience some premenstrual symptoms and 3-5% experience symptoms that meet the criteria for PDD.

Numerous scientific studies have shown that the menstrual cycle influences food intake. Healthy women consume 90-500 Kcal/day more (mainly provided by CHO in the form of bread and sweet foods) during the luteal phase than during the follicular phase. In women with PMS, results are similar with premenstrual increases in CHO, fat and protein intake. The reasons for this are unknown although changes in sensitivity to sweet and bitter tastes have been identified, and energy expenditure (basal metabolic rate) is known to be increased during the luteal phase. During PMS there is evidence for increased intake of pleasant-tasting foods. Food cravings appear to increase during the luteal phase of the menstrual cycle.

Menstrual distress and the symptoms of PMS have been associated with specific patterns of food intake but not many prospective studies have been carried out. Links have been identified between CHO intake and symptoms related to the menstrual cycle but no conclusions can be drawn. Severe premenstrual symptoms have been linked with a craving for and the consumption of sweet foods (particularly chocolate) but a carbohydrate rich-protein poor (CR-PP) evening meal containing 112 grams of CHO, 6 grams of protein, and 16 grams of fat appeared to mitigate such symptoms.

In another study, a specially prepared, carbohydrate-rich formula known to increase the serum TRP concentration reduced symptoms of PMS within 90 minutes to three hours after ingestion. It has been hypothesized that CHO consumption may reduce symptoms of PMS by stimulating the synthesis of 5-HT in the brain. It has been claimed that TRP itself can mitigate the symptoms of PMS but no placebo was used in this study.

WORK AND EXERCISE

In restrained eaters, a higher workload is associated with the intake of more lipids, expressed as percentage of total energy, but also more saturated fats, sugar and total energy intake. In those conditions, a high workload may be considered as a stressor and restraint as a disinhibitor.

Work and exercise induce many changes typical of stress with activation of various endocrine glands, including the anterior pituitary, the adrenal medulla and cortex, and the thyroid. Heart rate, blood pressure, breathing frequency and total ventilation all increase, and more energy is consumed as a result of the muscular activity. In addition, during and after intensive exercise, there are profound effects on blood flow, the intestinal secretion of vasoactive substances, and the function of the mucosal immune system in the gastro-intestinal tract.

All these changes are paralleled by increased food intake and often changes in what is eaten.

Laboratory animals which have been thoroughly habituated to a high work load on a treadmill consume more food and their adrenal glands contain higher levels of cortisol and catecholamine-synthesising enzymes, and reduced levels of catecholamine-degrading enzymes. They were also leaner than control animals. Lipolytic activity in muscle and adipose tissue and lipid turnover rates were increased due to adaptation to the high work load.

In human subjects, the character, duration, frequency of work have diverse adaptive effects on the organism. Both dynamic and static work increase energy output and food intake (and affect the selection of foodstuffs). In highly specialized workers such as female gymnasts, the nature of the work itself requires that the body remains as lean as possible with practically no fat which would compromise performance. This kind of profession may lead to eating disorders with highly restrained eating and it has actually been shown that the calorie intake of young female gymnasts during training is often lower than their estimated basal metabolic rate. Moreover, their protein, fat and CHO intakes were far from the Recommended Daily Allowances (RDA), and the daily distribution of their food intake was irregular despite the fact that they were training and performing at a high level. There was a remarkable degree of variation between individuals, an observation which has been corroborated in other studies on the effects of extremely hard work or exercise. Thus, it seems that there is an adaptive response to a very high work load which can result in special eating habits and which also modifies the body's energy economy.

But long term observations of subjects with moderately heavy work loads show that calorie intake more or less corresponds to energy output, and a proper energy balance can be established within two to three days. This particularly applies to work of a dynamic and/or intermittent nature. Thus, the response – including the amount of food consumed – is dependent on adaptation to a specific work load.

VEGETARIANISM

A subject's psychological state profoundly affects his or her eating behaviour, psychological well-being was associated with a thriving life and dietary satisfaction, whereas low self esteem can underlie eating disorders or other reward-seeking behaviour patterns.

Studies on vegetarianism have given inconsistent and sometimes contradictory results. Today, vegetarianism is an attractive option for many by virtue of a wide range of nutritional, medical, social and psychological factors. One approach has addressed the beneficial effects of a vegetarian diet, and another has analysed vegetarians' subjective reasons for adopting this kind of diet and its impact on their personal well-being. Together, these two lines of studies identify vegetarians as physically healthy, socially conscious individuals.

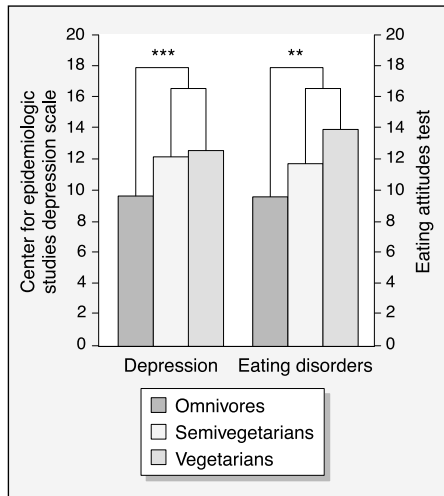


Figure 8. Psychological well-being and vegetarianism in women (reproduced from Lindeman).
 *** $p < 0.001$; ** $p < 0.01$.

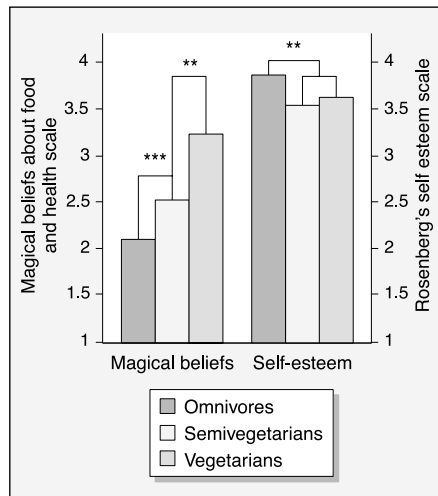


Figure 9. Vegetarianism and psychological well-being in women (reproduced from Lindeman. *Eating Disorders* 2000; 8: 157-65).
 *** $p < 0.001$; ** $p < 0.01$.

However, a third approach has addressed the psychological characteristics of vegetarians and this paints a different picture. In comparison with omnivores, semi-vegetarians and vegetarians have a greater incidence of depression and eating disorders (*figure 8*) and may have magical beliefs about food; self esteem was lower among vegetarian and semi-vegetarian women (*figure 9*); semi-vegetarians tended to be less satisfied with their appearance but all groups had the same level of satisfaction with respect to their weight. Other studies have shown that vegetarians are more likely to suffer from depression and anxiety. One study on vegetarianism and world assumption showed that vegetarian women had lower opinions about the benevolence of people and of the world in general, and also about control, justice and their own worth than did non-vegetarian and omnivorous women.

In many respects, vegetarians and semi-vegetarians can be less psychologically stable than omnivorous women. These findings raise a question about the vegetarianism: is it a healthier but an unhappy way of life? But the causality of the relationship has not been defined – is psychological instability a consequence of a vegetarian diet or the reason for adopting it?

STRESS, ENERGY BALANCE AND BODY WEIGHT REGULATION

In adult humans, body weight appears to be controlled in an extremely precise way by finely tuned regulatory mechanisms that keep the energy balance (between intake and expenditure) in equilibrium over long periods of time. Body weight, however, is not totally stable throughout the course of human life. Between the ages of 20 and 60, it increases by about 10 kg on average. This change actually demonstrates how perfect these energy balance mechanisms are: gaining 10 kg in weight over 40 years means that calorie intake very slightly exceeds energy expenditure (by a factor of 5 Kcal a day).

Thus, the energy balance is tightly regulated which raises a number of questions: what mechanisms are responsible for this regulation and what is the role of stress, not only in relation to food intake, as dealt with above, but also on the neuroendocrine networks involved in the control of body weight and body fat distribution?

ENERGY BALANCE

An essential role in the regulation of energy balance is played by the brain circuits which control energy intake and expenditure. These networks receive peripheral signals when the status of the body's energy reserves changes. After processing, they are converted into messages to stimulate the production of the effector molecules which control food intake and energy expenditure, thereby preventing excessive fluctuations in the level of energy reserves (white fat reserves). Among the molecules which are capable of carrying messages about changes in the status of the fat reserves to the brain are leptin and the corticosteroids. These hormones, whose levels vary with the amount of body fat, have been reported to influence the regulation of energy stores. Many different systems are

involved in controlling food intake and thermogenesis and the system probably contains significant redundancy. Some of the key factors are neuropeptide Y (NPY) thyrotropin-releasing hormone (TRH), melanin-concentrating hormone (MCH), pro-opiomelanocortin (POMC), agouti-related protein (AGRP), and cocaine-/amphetamine-regulated transcript (CART). These energy balance circuits also depend on the corticotropin-releasing hormone (CRH) system which plays a central role in the regulation of energy balance. Laboratory experiments have demonstrated that CRH is involved in the anorectic effects of treadmill running, oestradiol, caffeine and restraint-mediated stress, as well in the thermogenic action of serotonin receptor agonists and fenfluramine.

In the brain, CRH can bind to two types of receptor, CRH1-R and CRH2 α -R, and is inactivated when it is bound by the CRH binding protein (CRH-BP). The genes encoding the CRH-Rs are induced by stressing conditions. A new peptide termed urocortine (UCN) has a higher affinity for CRH2 receptors than does CRH itself. Like CRH, UCN decreases food intake and increases energy expenditure.

Leptin also reduces energy intake and energy deposition and stimulates thermogenesis in brown adipose tissue – this is all consistent with the possibility that the effects of leptin on energy balance are actually mediated *via* the CRH system. Leptin may inhibit CRH release and pituitary and adrenal secretory activity although, when leptin is deficient or non-functional, the hypothalamic pituitary adrenal unit is hyperactive. CRH2 α -R mRNA is expressed more when food intake is increased, and less when it is decreased. The importance of CRH deficiency in obesity has been highlighted in a number of different experiments.

In summary, there is more and more experimental evidence to suggest that this is controlled by a negative feedback loop in which glucocorticoids stimulate leptin production which, in turn, inhibits glucocorticoid secretion; in an acute context, leptin mediates an anorectic effect (both by stimulating CRH and by inhibiting NPY release) whereas, in a chronic context, it prevents activation of the HPA-axis.

In obese *fa/fa* Zucker rats, the acute effect of food deprivation is to stimulate the HPA-axis *via* CRH1-R and elicit stress-like effects, and on the other hand leads to a positive energy balance *via* CRH2 α -R. These findings may be due to leptin deficiency in these animals. In the same way, leptin resistance in obese patients might result in potentiated CRH activity and increased NPY release leading to an increased feeding drive with, as consequences, chronic disinhibition and overdrive of the HPA-axis.

BODY WEIGHT AND WEIGHT LOSS

Since the activation of the HPA-axis (by cortisol and/or corticosterone) results in anorexia and the inhibition of thermogenesis, it would seem logical to infer that stress may tend to promote a positive energy balance (as mentioned above). In animals, this is backed up by the well established fact that adrenalectomy blocks the development of obesity in all experimental model systems. Glucocorticoid administration to adrenalectomised rats

antagonises the effects of leptin in a dose-dependent manner. Thus, the effects of leptin on food intake and body weight are strongest in the absence of these hormones which would thus appear to be important in the control of body weight. Stress-induced glucocorticoids have long been believed to play a role in the development of obesity, including in humans with abdominal-type obesity. Intracerebral administration of glucocorticoids had a range of different effects: a marked, sustained increase in both food intake and body weight; high blood concentrations of insulin, leptin and lipids; a pronounced decrease in the expression of uncoupling proteins (UCP) 1 and 3; increased hypothalamic NPY; and decreased CRH levels.

In both animals and humans, mild stressors appear to induce circadian variations in corticosteroid levels and increased fat storage and lead to the metabolic syndrome. In agreement with this, studies in humans have suggested that there is a link between weight gain and exposure to various stress factors.

In a clinical context, a relationship has been found between changes in feeding behaviour and plasma cortisol levels. Furthermore, it has been reported recently that an increase in hunger, the desire to eat, and the prospect of food consumption significantly correlate with an increase in plasma cortisol at the point at which obese subjects become resistant to further fat loss (under a fat loss of 14% in men and 10% in women) in weight reducing programs.

Preferences for sweet and fatty foodstuffs have been studied with an analysis of taste responses in normal, obese and formerly obese individuals. Obese subjects preferred high-fat foodstuffs that contained less than 5% sucrose, while formerly obese subjects (reduced obese) showed enhanced responsiveness to both sugar and fat; normal subjects tended to prefer foodstuffs which contained less lipid and more sucrose. However, dietary restraint and the amplitude of weight fluctuations may be important environmental variables influencing food consumption patterns and the response to diet. When obese subjects were not recruited from a population interested in participating in a weight reduction programme but instead came from a non-clinical sample, the only differences observed were not between obese and lean subjects but between stable obese subjects and obese subjects with large weight fluctuations (*i.e.* patients with chronically restrained eating behaviour) who showed a preference for sweeter, higher-fat foodstuffs.

Other unexpected data have shown that the intensity of hunger is lower in subjects who take vitamin and mineral supplementation and also in those who have lower body weight, lower fat mass and a higher basal metabolic rate.

Some other unexpected consequences of dietary restraint in obesity are relatively common: recently, it has been shown that weight loss increases the concentrations of organic pesticides and PCBs in the plasma and subcutaneous adipose tissue of obese subjects – this is dependent on local lipolytic activity. This could be dangerous and might explain the increased mortality rate in patients who have lost weight. It could also have other effects such as the inhibition of thyroid function which could interfere with the basal metabolic rate (the higher the plasma organochloride concentration, the greater will be the

decrease in basal metabolic rate induced by the weight loss). These results raise concerns about undesired and potentially harmful consequences of weight loss in some obese patients who might be more prone to health problems than leaner subjects as a result of their heavy organochloride load.

It is well known that weight loss can interfere with various metabolic functions and this picture might be exacerbated by other factors such as stress, pollution or micro-nutrient intake.

OBESITY AND BODY FAT DISTRIBUTION

Stress is generally considered as a stimulus of psychosocial nature that affects the HPA-axis and homeostatic mechanisms. Evidence is gathering that the activity of the HPA-axis is perturbed in many obese individuals, particularly those in whom an abdominal or visceral phenotype leads to a condition that could be defined as functional hypercortisolism. This appears to be the result of two distinct mechanisms. The first appears to be central in origin and is characterised by impaired ACTH dynamics (pulsatile secretion) and hyper-responsiveness of the HPA-axis to various neuropeptides and to acute or chronic stress (through interference with noradrenergic control of the CRH-ACTH system). Certain dietary factors may also be involved. The second appears to be peripheral in origin, in the liver and adipose tissue, and is characterised by predisposition to certain chronic diseases. Therefore, the positive effects of weight loss should be balanced against possible negative effects. Thus, the ideal body weight might be considered as a mid-point between extremes: subjects who shed fatty tissue by means of dieting may expose themselves to stress and secondary problems such as hunger, immune impairment, metabolic effects like a decrease in basal metabolic rate, fat oxidation (which would tend to make putting the weight back on more likely), or a decrease in the mineral content of bone tissue; at the other end of the scale, the main risks associated with high body weight are diabetes mellitus, hyperlipidaemia and high blood pressure.

In summary, the available experimental evidence suggests that positive energy balance and high body weight not only occur because the amount the subject eats is not matched to his or her activity level, but also depends on cortisol dynamics. Simultaneous increases in cortisol production and clearance can result in lowered plasma cortisol by virtue of several distinct factors, including changes in the enzymes involved in cortisol metabolism. In the light of this, the possibility that visceral fat gain might be a necessary adaptation to enhance cortisol clearance and thereby deal with stress is a hypothesis that deserves further investigation.

It has been shown that there exists a relationship between, on the one hand, variations in plasma and/or urine cortisol, adrenal volume and socioeconomic status, and, on the other hand, the tendency to accumulate fat in the abdominal area (expressed by sagittal diameter) and waist to hip ratios or visceral fat levels (as measured by CT scanning).

This correlation implies that people exposed to stress are more prone to deposit fat in the abdominal region, particularly in the visceral compartment.

Since the tendency to visceral fat deposition in response to overfeeding is known to have a significant hereditary component (as established in studies of overfeeding in homozygotes), there is interest in the genetic details of this phenomenon. Preliminary research in this area has shown that genetic variations in glucocorticoid receptor genes are associated with variable visceral fat deposition.

Many clinical studies have shown that abdominal obesity is associated independently with a low education level, unemployment and problems at work in both men and women. It is also associated with depression, anxiety, distress, and irritability (with exacerbation over time). In post-menopausal monkeys, social status affects body fat distribution with dominant monkeys having more abdominal deposition. However, in intact (non-ovarectomized) monkeys, social subordination (a stressor) is associated with a central pattern of fat distribution.

Interestingly, several studies have shown that stress and psychiatric and behavioural problems are associated with central fat deposition suggesting that a link may exist between the physiological and/or metabolic consequences of stress, central and, in particular, intra-abdominal deposition of fat, and health. Higher levels of cortisol metabolites have been measured in depressed men (but this is not related to adiposity in either sex) and central obesity in men (but not in post-menopausal women) has been shown to be associated with enhanced pituitary-adrenal responses to CRH – this correlation was observed in depressed and non-depressed subjects alike. In reality, most subjects with visceral obesity and insulin resistance have no depressive symptoms and their HPA-axis functions completely normally: it might be a result of increased glucocorticoid sensitivity in the target tissue due to polymorphism of the receptor, but other genes involved in glucocorticoid metabolism might be important as well.

However there is some overlap between patients with chronic stress and depressive symptoms and those with central or visceral obesity combined with insulin resistance. This clinical picture has been described as pseudo-Cushing's syndrome since there are marked clinical, physiological and biochemical similarities between acute stress and melancholic depression syndrome. Both conditions are associated with hyperactivity of the HPA-axis and the locus caeruleus/noradrenaline system, and therefore, increased secretion of CRH, cortisol and catecholamines. This results in inhibition of growth, thyroid function and the reproductive system, in suppression of the immune system, increased interleukin-6 production, and marked osteoporosis.

Changes in HPA-axis function in subjects with abdominal obesity are also associated with insulin resistance. By analogy with clinical syndromes due to excess glucocorticoid production (*e.g.* Cushing's syndrome), this suggests that these hormones may play a role in the relationship between visceral obesity, the metabolic effects, and the predisposition to metabolic and cardiovascular disease.

EXERCISE AND CHANGES IN BODY WEIGHT

Intense, prolonged physical exercise may induce the generation of high levels of reactive oxygen intermediates – this is supported by the fact that such exercise is associated with lipid peroxidation and damage to skeletal muscle.

Apart from this effect related to the well-characterised phenomenon of oxidative stress which is not being dealt with in this text, physical activity is known to be a metabolic stressor. A significant number of facts suggest that the metabolic effect of physical exercise are due to a reaction to physical stress, and comprise acute intermediate metabolic adjustments at a molecular level in the skeletal muscle, liver, kidney and adipose tissue.

Prolonged, slow walking induces little metabolic, hormonal or cardiovascular stress, and the greatest perturbation at rest appears to be due to increased fat oxidation and the mobilisation of free fatty acids in plasma as a result of a combination of increased lipolysis and decreased esterification. Limited periods of more intense exercise stimulate increased oxidation of glycogen and triacylglycerol. Furthermore, these intramuscular reserves of CHO and fat appear to be the most important substrates in the kind of enhanced oxidative activity and performance developed by endurance training (which increases the density of mitochondria in muscle tissue). Acute exercise (*e.g.* weight lifting) that results in rapid fatigue involves the stimulation of many different muscle fibres and work on the part of many motor units at the same time. Such effort has a profound effect on protein synthesis in muscle tissue and enhances neuromuscular function.

Continuous aerobic activity with moderate to high caloric expenditure is an effective means of reducing body mass although the exact energy expenditure is difficult to quantify and control. Aerobic exercise also stimulates lipid metabolism, improves blood pressure, generally helps cardiovascular function and leads to the loss of fat. A combination of exercise and a suitable diet represents a flexible and effective approach to weight loss. Exercise stimulates the mobilisation and utilisation of lipids.

The results of studies over the last few years have shown that metabolic responses to physical stress are dependent on genetic factors, particularly with respect to the ACE gene. However, it could be imagined that traits which vary enormously from one subject to another such as the capacity for physical effort, responses to physical training, and the ability to perform would be multifactorial at the genetic level, *i.e.* involving many different genes.

STRESS AND NUTRITION IN PATHOLOGICAL SITUATIONS

It is well recognised that pathology and nutritional status are intimately inter-linked with disease and malnutrition often constituting a vicious circle. Rigorous epidemiological studies have shown a relationship between nutritional deficiency and the rates of morbidity and mortality due to infectious disease, pointing to the effect of inadequate protein and calorie absorption on immune function. Other recent investigations have revealed that inflammatory processes play a central role in the determination of nutritional status and its prognosis.

METABOLISM AND BODY COMPOSITION DURING STARVATION AND MALNUTRITION

Two different situations may be observed: the first is simple, non-stress starvation or uncomplicated fasting; the second is stress starvation. Simple, non-stress starvation results from the complete or partial interruption of energy intake for a variable period of time. Humans adapt well to starvation, using glycogen for a short period, then mobilising fat and protein reserves. At later stages, energy expenditure is reduced and protein tends to be preserved. Hormonal changes lead to glycogenolysis first and then lipolysis with the release of fatty acids and glycerol into the blood. The glucose requirements of the brain and the red blood cells are supplied first from glycogenolysis and later from gluconeogenesis in the liver and kidneys (*figure 10*). With prolonged starvation, the rate of gluconeogenesis from amino acids drops and protein is conserved by slowing down the metabolic rate (by 10-15%) together with an adaptive response by the brain which begins using ketones for energy.

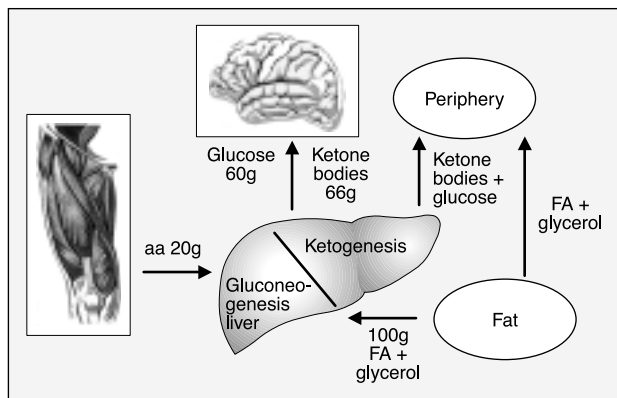


Figure 10. Metabolism in uncomplicated fasting (7 days) (reproduced from Sobotka). aa = amino acids; FA = fatty acids.

The effect of simple fasting (with no nourishment apart from non-caloric beverages) on body composition has been investigated in obese male subjects for a period of 14 days. Absolute fasting led to a significant decrease in body mass and fat mass, and in intracellular and extracellular water volume. On the basis of measurements of nitrogen levels in the urine, the rate of protein loss in the first week was greater than that in the second – this corresponds to the adaptive protein-sparing response to non-stress fasting. Resting energy expenditure decreased by 13% while lean body mass decreased by only 7%, again reflecting metabolic adaptation. Fat oxidation increased after the end of the fasting period whereas glucose and protein oxidation decreased (*figure 11*).

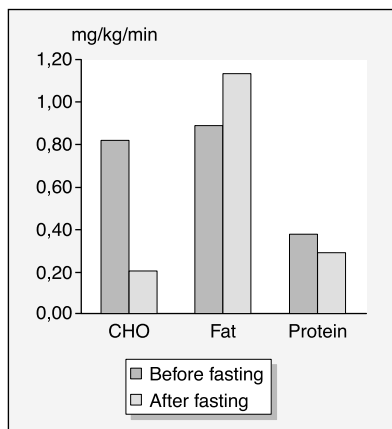


Figure 11. Basal substrate oxidation (reproduced from Sobotka).

Stress starvation is a response to a combination of starvation and stress (frequently inflammatory stress). In early studies, kwashiorkor was supposed to be exclusively due to low protein intake. However, in times of severe stress, kwashiorkor can develop within a few days. The paradox of the metabolic response to stress or injury is that it is essential to provide the substrates necessary for survival but, in extremes cases, this can

result in such a level of dysfunction and tissue loss as to jeopardise survival. Substrates are released from muscle tissue, fat, bone and organs for use in processes which are necessary for the subject to overcome the effects of acute illness or trauma such as tissue regeneration, the synthesis of essential mediators and the generation of antioxidant species.

In response to the stress, large amounts of adrenaline, glucagon and cortisol are released. These hormones induce lipolysis, gluconeogenesis and extensive breakdown of the body's protein. It has been shown that the rate of lipolysis in white fat tissue is increased in experimentally stressed rats and this is associated with heightened sensitivity to catecholamines, attenuation of $\beta 1$ adrenergic receptor-mediated responses and potentiation of $\beta 2$ adrenergic receptor-mediated responses.

Amino acids released from body protein (mainly derived from muscle tissue) are used for the synthesis of acute phase reactants and clotting factors as well as for gluconeogenesis and healing processes. Stress is associated with decreased plasma glutamine levels which ultimately results in immunosuppression since this amino acid (together with others such as arginine is a major source of energy for activated immune cells. Glutamine is also important in the turnover of the cells of the intestinal mucosa and in the defence against bacterial invasion. Electrolytes are mobilised from the intracellular environment and from bone tissue and excreted in the urine in order to maintain adequate sodium and preserve the body's acid-base balance.

One of the most typical features of both stress starvation and kwashiorkor is a sharp decrease in albumin concentration in association with oedema. The oedema is due to the diffusion of water, electrolytes and albumin into the extravascular compartment, and results in an increased body weight and total water content because of expansion of the extracellular fluid volume (although the intracellular water volume and cell mass decline).

Thus, the changes in body composition seen in stress starvation are more striking than those seen in simple starvation. Simple starvation is associated with adaptive, protein-sparing responses whereas stress starvation results in muscular wasting, fluid retention and oedema. It can be anticipated that kwashiorkor – which in the past was attributed to simple protein deficiency – is actually the result of a combination of stress and starvation. The catabolic state induced by stress starvation cannot be reversed by nutrition alone although adequate nourishment is essential in order to avoid malnutrition-related problems.

MALNUTRITION, FEEDING BEHAVIOUR AND HOSPITALISATION

Malnutrition is a major public health problem, not only in developing countries but also in affluent countries, particularly in hospitalised patients, where it is estimated that between 30% and 50% are malnourished. Undernutrition is largely unrecognised on admission and tends to deteriorate in the course of the hospital stay. Malnutrition can be defined as deficiency in caloric intake, or in the intake of protein or any other specific nutrient, which produces a measurable change in body function. It prejudices the chance of recovery from

concomitant disease and can be corrected by nutritional therapy. Although malnutrition is associated with increased morbidity and mortality, too little attention is paid to it by health professionals.

Furthermore, hospitalised patients are often anxious and may be stressed. As discussed previously, studies in humans concerning the influence of anxiety on feeding behaviour have yielded disparate results with increased food intake observed in some cases, decreased intake in others, and no change in some. Animal studies suggest that stress may directly influence the basic behaviour patterns which are mediated by the dopaminergic system such as appetite.

An investigation was conducted to analyse how anxiety might affect food intake during a short hospital stay (2 to 15 days). Anxiety was assessed using the State-Trait Anxiety Inventory Scale. During hospitalisation, mild anxiety was quite common. The group of patients who ate the least (less than 75% of the offered food) were significantly more anxious than those who ate more normally (*figure 12*). State anxiety (interpreted as actual anxiety), but not trait anxiety (interpreted as usual anxiety) in men correlates negatively with food intake. Given the prevalence of malnutrition in hospitalised patients and its relation to mortality and morbidity, more attention ought to be paid to food intake and, perhaps, more effort should be put into mitigating the patients' anxiety.

Finally, since so many cases of malnutrition remain undetected, all hospitals should institute systems for screening the nutritional status of patients on admission.

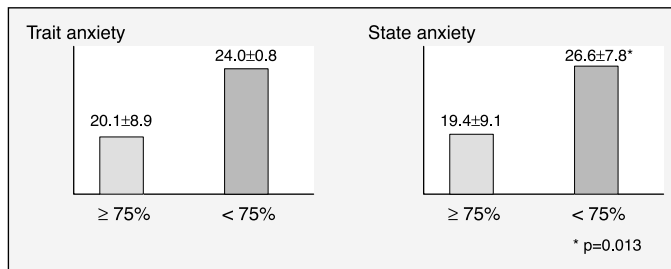


Figure 12. Food intake (normal: $\geq 75\%$ vs abnormal: $< 75\%$) and the State Trait Anxiety Inventory Scale in hospitalised patients (reproduced from Planas).

STRESS AND INFLAMMATORY BOWEL DISEASE

Idiopathic inflammatory bowel disease (IBD) encompasses Crohn's disease and ulcerative colitis, the most common and serious chronic inflammatory conditions of the bowel in humans. These diseases are currently thought to result in genetically predisposed subjects when a number of environmental factors converge. The natural course of IBD is episodic and some patients claim that the disease first occurred during a time of emotional stress or that stressful events precipitate flare-ups. This could be due to stress inducing either the expression of symptoms or reactivation of the disease. Whether or not there really exists any link between flare-ups of IBD and stress remains controversial. Early studies

concluded that there was a temporal relationship but others failed to find any such correlation. For example, ulcerative colitis was first described in Bedouin Arabs after they had been moved to government housing and it was attributed to social stress. Gibbons subjected to social stress develop a fatal form of colitis. Similarly, the colitis which affects cotton-topped tamarins living in cages has never been found in captive monkeys in natural-type enclosures or in wild animals.

Current knowledge of the scope of interactions between the nervous and immune systems provides a plausible basis for further considering a causal relationship between stress and inflammation of the bowel. It has been shown that inflammation in the gut is influenced by the release of cytokines IL-1, IL-6 and TNF. Stress is known to affect IL-6 production and both endogenous and exogenous corticosteroids have been shown to significantly decrease production of a host of pro-inflammatory cytokines, including IL-1.

In a preliminary experiment on rats, colitis was induced by the administration of a chemical enema and then the animals were subjected to restraint stress. The restraint stress caused significant inflammation in animals with pre-existing inflammation of the bowel and this was associated with more profound inhibition of noradrenaline release and IL-1 messenger expression in colonic tissue than that measured in either of two other groups, namely non-stressed animals with pre-existing inflammation, and stressed animals with no pre-existing inflammation.

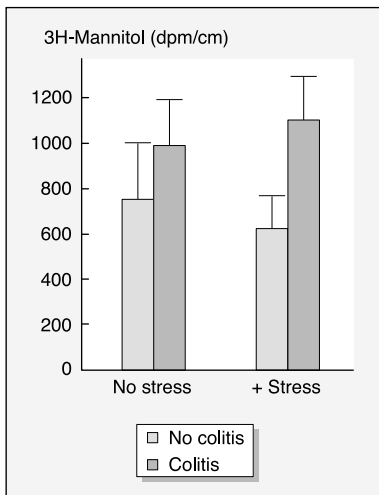


Figure 13. Effects of stress on colonic permeability (reproduced from Qiu *et al. Nature Med* 1999; 10: 1178-82).

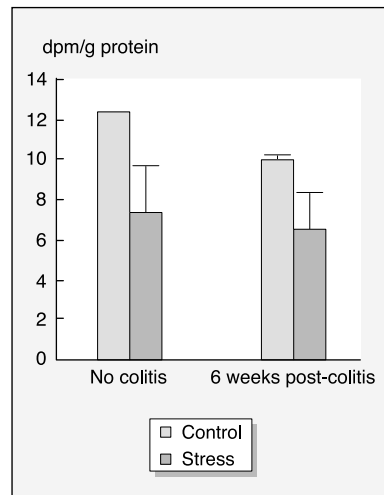


Figure 14. Effect of stress on colonic mucin production (reproduced from Qiu *et al. Nature Med* 1999; 10: 1178-82).

This clearly shows that established inflammation renders the colon more susceptible to the effects of stress on enteric nerve function and inflammatory mediators. In a second experiment in which colitis was chemically induced in mice, after the initial inflammation stress, a very low dose of the inflammatory agent could produce significant colitis; this effect was not observed when the same dose of the inflammatory agent was introduced into normal animals.

Furthermore, in these animal models, colon permeability was increased (*figure 13*) and less mucin was produced (*figure 14*). In euthymic mice, an increase of the effect of stress + hapten on quiescent inflammatory colitis is observed, in comparison with athymic mice.

The susceptibility to stress reactivation has been shown to require the presence of CD4+ or CD8+ lymphocytes. Hence, the stress reactivates colitis by facilitating the entry of luminal contents that activate previously sensitised CD4 cells in the gut. Cytokines, particularly IL-1, may play a role in changing both the permeability of the gut mucosa and the sensitivity of the immune system following stress. Susceptibility to stress can be adoptively transferred (*via* CD4+ or CD8+ T cells) and this reactivates colitis.

Thus, susceptibility to stress has specific, immunological prerequisites. Stress management should be an integral part of the treatment of IBD.

SOME POINTS ON COMBATTING STRESS

There is no single approach for fighting against stress or mitigating its effects. Some examples are given here, but these should not be considered as a comprehensive list of all the possibilities in this complex but fascinating area.

OXYTOCIN

It is hypothesised that there is an active anti-stress system with a psychophysiological profile opposite to that of the stress system which is mediated by the HPA-axis and the sympathetic nervous system. The physiological functions of the stress system are to induce adaptive metabolic and behavioural changes characterised by arousal and aggression. In this reaction pattern, CRH and vasopressin are important regulators at the hypothalamic level.

Oxytocin (OT) is not only produced in the paraventricular nucleus of the hypothalamus but also in the autonomous neurovegetative system centres linked to the spinal cord. In opposition to the stress system, OT integrates a physiological anti-stress pattern characterised by quiet and calm, and slowing down motor behaviour, as seen during breastfeeding; this effect is due to activation of the vagal nerve as evidenced by increased levels of insulin and cholecystokinin. OT not only has this anxiolytic effect, but also lowers blood pressure and cortisol levels, and elevates the pain threshold (as measured by tail flick latency in rats), and may increase weight without increasing appetite (in female rats and in young rats). In addition, it is linked to stimulation of growth and healing. OT has been shown to stimulate various kinds of positive interaction (maternal, sexual and social behaviour) and may also promote bonding. The long-lasting, anti-stress effects induced by OT seem to be

mediated by an increase in both the number and the activity of central α -adreno receptors. These receptors act as inhibitory auto-receptors in noradrenergic and adrenergic neurons in the brain and also post-synaptically, *e.g.* in the brain stem and medulla. Modifying the balance between α 1- and α 2-receptors and giving predominance to the α 2 family of adrenergic receptors seems to mediate an anti-stress adaptation, and introduces a buffering system. Oestrogen and cortisol may activate the OT gene. In the presence of OT, dexamethasone does not induce leptin (which induces anorexia and increased energy expenditure). But whether the anti-stress pattern induced by OT is linked to a strengthening of the immune system remains to be established. This is an "ancient" system for energy conservation and for ensuring the well-being of mother and child (suckling and also caressing may stimulate OT in women and OT has been found in breast milk). It could be said that OT is an "altruistic" peptide in contrast to vasopressin.

STRESS-RELIEVING BRAIN-FOOD

L-tyrosine

L-tyrosine, the precursor for NA and DA, enhances NA synthesis and this prevents stress-induced NA depletion in the animal brain.

In humans subjected to a physical stress consisting of a 90 dB noise, 100 mg/body weight of tyrosine improved short term memory, accelerated decision-making and decreased diastolic blood pressure without any effects on mood, systolic blood pressure or heart rate. In another experiment, the effects of tyrosine on fatigue and stress during two weeks of combat training (including sleep deprivation, food rationing, exposure to cold and humidity, high physical demands and stress) were studied with a formula containing 42 grams of protein and 2 grams of tyrosine. Assessments were made both immediately prior to the combat course and on the sixth day of the course. The group supplied with the tyrosine-rich formula performed better on a memory (*figure 15A*) and a tracking task (*figure 15B*) than the group supplied with a CHO-rich drink.

These findings suggest that, in times of psychosocial and physical stress, supplementation with tyrosine may reduce the effects of stress and fatigue on cognitive task performance, with no known disadvantages. But further studies into the effects of tyrosine are needed.

Serotonin-inducing diets

Serotonin (5-HT)-inducing diets refer to balanced amino acid-supplemented formulas with tryptophan (TRP) and CHO rich/protein poor (CR/PP) diets, as opposed to formulas supplemented with amino acids not including TRP and CHO poor/protein rich diets.

Reduction of 5-HT levels selectively impairs memory consolidation and lowers mood in vulnerable subjects. Stress-vulnerable subjects who received a CR/PP diet or a

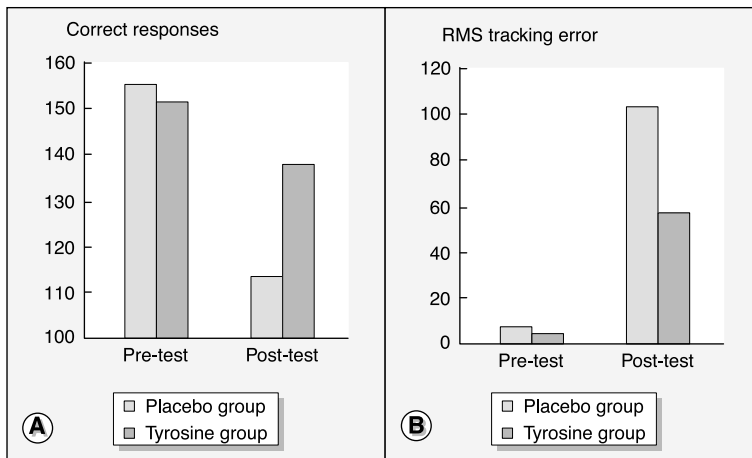


Figure 15. The effects of tyrosine on cognitive functions during sustained operations. A: Memory comparison task. B: Tracking task (reproduced from Deijen *Brain Res Bull* 1999; 48: 203-9).

high-protein, TRP-enriched diet which increased peripheral markers of 5-HT was beneficial with respect to mood and memory performance.

The probability of low 5-HT levels in the brain is probably greater in subjects who are vulnerable to stress and also exposed to it. Psychological stress increases the need for 5-HT synthesis and therefore the need for TRP in the brain; unfortunately, through physiological pathways, stress directly limits the availability of TRP in the brain. Nevertheless, subjects who are particularly prone or exposed to stress might benefit from a diet designed to make TRP available.

In depressed patients and their close relatives (without the symptoms), patients with irritable bowel disease (IBD) and MDMA (ecstasy) abusers, the 5-HT system may be deregulated. In depressed patients, vulnerability is genetically determined; in patients with IBD, it is probably peripheral as well as central; and serotonergic toxicity may be the reason in MDMA abusers. For all these groups, the hypothesis is that a diet which increases brain 5-HT may be able to mitigate the symptoms. But the mechanisms involve not only the entry of TRP into brain, but also the conversion of about one per cent of it into melatonin which may reduce fatigue.

In a recent study, the effect of a diet based on lactalbumin (which has the highest tryptophan concentration of all bovine protein fractions) was assessed and compared to one based on casein. The consumption of TRP-rich dietary protein increased the plasma TRP-large neutral amino-acid ratio and, in stress-vulnerable subjects, decreased the level of cortisol, reduced depressive feelings, improved memory search (*figure 16*) and coping ability with stress by increasing serotonin that may subsequently reduce the cortisol response. Simultaneously, in those subjects, it increased the concentration of prolactin, the secretion of which is regulated by serotonergic mechanisms in the brain, that is an index of the hypersensitivity of the serotonergic system.

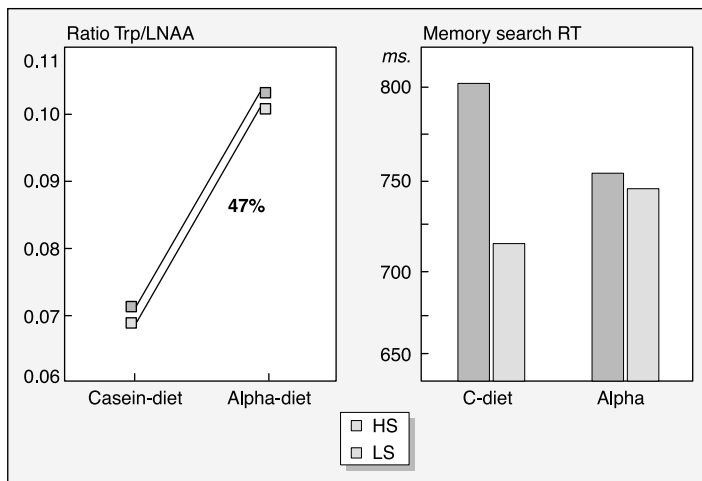


Figure 16. Tryptophan-enriched protein alpha-lactalbumine improves memory search in 58 stress-prone subjects (reproduced from Markus *et al.* *Am J Clin Nutr* 2000; 71: 1536-44).

PROBIOTICS, AND THE IMMUNE AND GASTRO-INTESTINAL SYSTEMS IN EXERCISE

Increased attention has been focused on the possible role of the gastro-intestinal (GI) system on the health and performance of athletes. Intense exercise has been shown to have a series of immediate consequences in athletes: lower GI tract symptoms, negative impact on GI quality of life and on composition of intestinal flora, impaired immune function (decreased activity of IgA-producing cells reduced numbers of T lymphocytes, NK cells, and salivary antibodies and reduced INF- γ production) and an increased incidence of upper respiratory tract infections, reactivation of viral infections, and the establishment of opportunistic infections. This was particularly true in athletes with increased mucosal interactions with antigens and allergens during episodes of intensive physical exercise. There is evidence that specific nutrients and food compounds act as critical factors in the expression of the GI as well as the systemic immune response. This action is linked to the interactive relationship between digested nutrients, the intestinal flora and the status of the immune cells which is in turn dependent on which cytokines and growth factors are present.

Stressed athletes might gain benefit – in terms of their capacity to tolerate the stress and their immunocompetence – from specific biological preparations, such as probiotics. Probiotics are specially selected live lactic acid bacteria (LAB) such as *Lactobacillus* and *Bifidobacterium*.

It is expected that regular ingestion of a suitable quantity of LAB will stimulate local GI immunity with mucosal antibody production, especially of IgA by PP cells. In addition, probiotics have been shown to enhance phagocytic function, increase T lymphocyte numbers, and stimulate the production of INF- γ and IL-6 by peripheral blood lymphocytes.

In a preliminary study, immunocompetence was assessed in endurance athletes after the consumption of a *Lactobacillus* probiotic strain with 10^9 microbes/d: it had no influence on performance parameters or muscular stress responses but mitigated the post-exercise drop in NK cell numbers, increased the resting levels of NK cells in the regeneration period, and induced changes in the faecal flora with a reduced density of *Bacteroides* spp. and an increased density of *Enterococcus* spp. The effect of probiotic supplementation in symptomatic runners from a group of screened athletes should be investigated. In a second study, it was shown in a logistic model that physically stressed athletes had a reduced GI quality of health.

BEHAVIOUR AND COGNITIVE INVOLVEMENT

Foodstuffs preferred by emotional eaters under stress tend to be highly palatable, easily eaten snack items that are low in protein. Such foods have been shown to protect stress-prone people from adverse consequences of acute stress as to physiology and mood. These patterns suggest that, for some people, psychological traits and neuro-hormonal susceptibility may reinforce habits of choosing unhealthy high-caloric snack foods during stress.

It would be preferable to develop another way of coping with stress. How food cravings can be abolished by strengthening the correction with the environmental conditioned stimulus has been demonstrated in the context of binge eating. This suggests that mood-related cues, including stress, may also contribute to the development of food cravings through associative conditioning and negative reinforcement.

It has also been demonstrated that cognitive involvement focuses attention on the most salient stimuli, allows sensory stimuli to elicit eating while “diet monitoring” is suppressed and so, may decrease food intake in low restraint subjects, by reducing the emotional component (but not in high restraint subjects).

CHOCOLATE, AN “ANTI-STRESS FOOD”?

Craving for chocolate reflects a desire to consume a pleasant substance. A review of the literature on cravings suggests that the hedonistic appeal of chocolate (fat, sugar, texture and aroma) is likely to be a predominant factor in such cravings. It has been demonstrated that capsules containing the pharmacological ingredients of chocolate have an effect and that only chocolate itself can satisfy chocolate craving. A link has been reported between negative mood and chocolate craving, for example, chocolate intake increased when subjects were played sad music, while carob intake was not increased. Chocolate contains several biologically active substances, including the neurotransmitter precursors (phenylalanine and tyrosine), methylxanthines (caffeine and theobromine), biogenic amines phenylethylamine and tyramine and cannabiod-like fatty acids. It has been suggested that

the attraction of chocolate reflects an increase in serotonin production, the provision of methylxanthines, phenyl-ethylamine or magnesium. Chocolate may be used by some as a form of self-medication to balance low levels of neurotransmitters involved in the regulation of mood, food intake and compulsive behaviours (e.g. serotonin and dopamine). In a laboratory-based experiment, the effects of anger, fear, sadness and joy (induced by films) on hedonistic responses to chocolate were studied. During joy, hedonistic responses were higher than during negative emotions. Furthermore, the effects of emotion on hedonistic responses to chocolate were stronger than the effects of deprivation. Indeed there is little evidence to suggest that chocolate craving reflects any kind of physiological need. The drug-like substances within chocolate are unlikely to have any pharmacological effect because they are present at such low levels that it is not possible to consume physiologically active amounts. Furthermore chocolate contains too much protein to be able to stimulate 5-HT synthesis.

The most plausible biological explanation is that chocolate, in the same way as other palatable foods, induces the release of endorphins in the brain. Much of the evidence suggests that a craving for chocolate reflects a desire to consume a pleasant substance that may also stimulate endorphin release. Sweet fatty food items have a pleasant taste; chocolate approaches the ideal combination of sweetness and fat content. Pleasant-tasting foods induce the release of endorphins in the brain. Drugs that block endorphin activity decrease the effect of the intake of palatable foods such as chocolate.

CONCLUSION

According to Selye, stress results when the body is trying to cope with environmental, internal, physical or psychological insults by means of a series of non-specific responses and the body's basic homeostatic mechanisms are overcome. Therefore, stress is neither the triggering event nor the conditions which are causing the stress, although the word is often used to refer to these.

Stress may lead to responses that involve specific regulatory mechanisms which are designed to maintain homeostasis; however, the physiological response – which depends on both genetic and individual features – may induce deleterious changes which go beyond the original objectives. Stress-induced damage to physiological systems is a common reason for susceptibility to disease, although the importance of this factor in the onset of health problems is clearly often underestimated.

Nutrition and eating behaviour are very much at the heart of these questions because many different types of stress appear to affect food intake, and nutritional status may have a major impact on homeostatic mechanisms.

Stress is known to induce hypophagia, an effect which can be explained at both the biological level (*e.g.* CRH release), the behavioural level (*e.g.* priority is given to defensive action rather than eating) and the affective level (*e.g.* anhedonia). In contrast, stress can also result in increased food intake which appears to be the result of interplay between dopaminergic and opioid neurotransmitters. The link between stress and increased food intake has been intensely studied because of the possible role of emotional factors in obesity and other eating disorders. An important finding of this research is the distinction between restrained and non-restrained eaters: the former are more likely to display stress-induced hyperphagia whereas the latter report no effect or hypophagia (and the actual foodstuffs they choose to eat when under stress tend to change).

Nutritional influences on stress have mainly been investigated in the context of cardiovascular disease and, more recently, inflammation, infection and immunity. Nutritional

factors may play a role on the interaction between stress and inflammatory bowel disease. Various nutrients are particularly important in maintaining the immune system and mediating its responses, *e.g.* nutritional status is known to have a direct impact on viral load in certain forms of viral disease. Probiotics, in addition to nutrients, play an important role by modulating the health-promoting actions of intestinal bacteria and protecting the local flora against the adverse consequences of stress. Lastly, nutritional factors are able to modulate the body's metabolic processes and composition to mobilise the substrates necessary for the fight against stress.

Stress and Nutrition: a Fascinating Crosstalk

“Stress and Nutrition” was the focus of an international workshop organised by Danone Vitapole. To be nourished has always been an existential concern of the human being. Nutrition is a fundamental pillar of life, health and development across the entire life-span. In the same time, our eating behaviour is largely influenced by our sociological and cultural environment.

Stress can be of environmental as well as of physiological origin and many definitions of this term are possible. How do we interpret what we express by saying “I am stressed”? And which are the interactions between nutrition and this stress? Would it be that under stressful conditions we automatically tend to eat certain foods who might help us to better cope with the situation? Or do certain eating behaviours influence the stress-response and therefore have an impact on our health and well-being? Many questions still remain open.

With this scientific meeting, bringing together worldwide researchers, Danone Vitapole contributes to a better understanding of the interactions between metabolic pathways and central nervous system mediators, and the regulating processes that are important for an optimal functioning of our organism.



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