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SICKNESS BEHAVIOR IN FEVER AN HYPOTHERMIA

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1. ABSTARCT

Sickness behavior has become a common expression in the description of general symptoms of diseases and regarded as partly or fully advantageous for the patient to combat infection or other disturbance acting on the body. Several components of sickness behavior such as anorexia, sleepiness and inactivity have significant energetic connotations and hence may affect body mass and/or body temperature. Thermoregulatory accompaniments of sickness behavior could be either fever or hypothermia depending on the nature and severity of disease. A survey of the relevant literature has identified afferent, central and efferent mechanisms that may allow separate or coordinated appearance of behavioral and/or thermoregulatory aspects of these symptoms occurring under different experimental conditions. An attempt has been made to find some biological logic in the appearance of various components of sickness behavior and changes in body temperature that could explain the purported positive value of sickness behavior in disease survival.

2. INTRODUCTION

The bodily discomfort commonly called also as complaint, uneasiness, malaise just to mention a few terms has been known to sick humans and their doctors alike for millenia. The phenomenon of that discomfort has been variously attributed to physical weakness caused by the invading microbes *per se* and/or by the resulting limitation in various bodily functions such as circulation, respiration, muscular performance or even to the vague symptomatology of mental alterations. A new paradigm has been introduced recently with the description of the concept of sickness behavior as a common constellation of behavioral responses developing during sickness or ill-ness (1). Even more importantly, this syndrome of seemingly abnormal behaviors (e.g. sleepiness, anorexia, decreased motility, social withdrawal, depression) may be regarded as a means of helping the individual to survive an external disturbance (infection, trauma, etc.) acting on the body. Interestingly, an early formulation of this syndrome has been described as early as in 1784 by William Buchanan (2) as follows: "nervous fevers may be occasioned by whatever depresses the spirits or impoverishes the blood; as grief, fear, anxiety, want of sleep, intense thought, living on poor watery diet, unripe fruits, [etc.]". An important factor of sickness behavior identified recently as a phylogenetically old potentially useful response of animals and men to infections and psychic stress is fever (for reviews see 3, 4). A remarkable feature of both fever and the aforementioned other components of sickness behavior is their partly or completely interconnected nature appearing differently during various stages or forms of diseases with a wide range of etiologies.

Fever as a regulated rise of deep body temperature has been the subject of intensive research in the course of the last couple of decades; its afferent factors, central mediators and efferent thermoregulatory means resulting in an elevation of core temperature have been studied in detail. Autonomic and behavioral thermoregulatory mechanisms (i.e. appropriate changes in heat production, heat loss and/ /or operant and other ways of thermoregulatory behavior leading to increased heat production and heat conservation) have been analysed in numerous studies carried out in animals and humans (for reviews see 3, 5). In addition of being an unpleasant or even unbearable sign of diseases - together with other general symptoms (such as pain, nausea) - the phenomenon of fever could even represent a metabolic and circulatory burden to the organism especially in patients with limited metabolic and cardiorespiratory reserve. Still, apart from the latter cases or when febrile body temperature approaches extremely high levels, the idea of fever having some survival value has been a feeling among a number of medical practitioners first without any proof. The crucial experiment in support of fever as a means of survival came some 30 years ago when it was shown convincingly that lizards could withstand infections much better if they were allowed to select a high ambient temperature thus to achieve a febrile core temperature as opposed to lizards

Table 1. Some components of sickness behavior and thermoregulation helping the defence systems to fight infection or to repair eventual tissue injury

Component	Thermoregulatory relevance
Fever	Regulated rise in core temperature
Hypothermia	Regulated or passive fall of core temperature, the latter resulting from decreases in heat production and/or heat conservation
Inactivity	Decreased heat production from muscle thermogenesis other than shivering
Sleepiness	Centrally induced mild hypothermia in subacute inflammation
Anorexia	Decreased need for GI tract blood flow and metabolism
Social isolation	Avoiding psychological and sensory stress of high neuroendocrine regulatory need

without the possibility to warm themselves up when exposed to the same pathogen (6). Unequivocal evidence for the survival value of fever in mammals including humans is still lacking in the face of strong personal conviction and experience in favour of this notion.

The term ”sickness behavior” has gained wide acceptance in the field of pathophysiology, in general, and in behavioral or immunological research, in particular. In fact, much of the research carried out during the last 10-15 years helped establishing some by disciplines such as neuroimmunology and psycho-neuroimmunology. The nature of afferent information from the periphery triggered by infection or injury to CNS sites, origins of coordinated behavioral responses observed in the framework of sickness behavior, have been known. In addition to this, the existence of an extensive immunological network and/or parallel pathways of rapidly acting nervous afferent mechanisms have also been discovered (for a review see 7).

For the purpose of the present review on sickness behavior an attempt was made to select mainly those publications that reported on experiments in which behavioral responses were followed in connection to changes in temperature regulation be it either fever (regulated rise in body temperature) or regulated (or central) hypothermia. Information from the vast literature on immune mechanisms playing a role in sickness behavior were quoted mainly to illustrate their possible dependence on or independence from thermoregulatory changes including body temperature, autonomic thermoregulatory effectors or specific thermoregulatory behaviors.

3. COMPONENTS OF SICKNESS BEHAVIOR RELEVANT TO PATHOPHYSIOLOGY OF THERMOREGULATION

There is an impressive list of behavioral phenomena experienced regularly by sick patients or observed by their relatives, but a more careful analysis of the signs of diseases and their severity may also provide quantitative estimate of some behavioral indices, thus allowing the gradation of disease states. Behavioral parameters of sickness relevant to thermoregulation are fever or hypothermia, reduction in phys-ical activity that may save energy for other purposes such as the metabolic cost of fever (i.e. the energy needed for the develpoment of high core temperature), the energy cost of higher tissue temperature, the so called Q_{10} effect (see 8). In this context the substrate supply required for an immune burst (allowing release of humoral/cellular factors/mediators of inflammation) to combat infection could also be mentioned (Table 1). Economical usage of energy available for the purposes indicated above seems to be all the more important, since inactivity tends to limit purposeful movement to look for nutrients, so that a decrease of food intake, even anorexia belongs to the main symptoms of sickness behavior. It has been speculated that the sick individual’s anorexia is the consequence of inactivity and may be looked upon as a compromise under natural conditions when an animal fighting against infection is forced to hide to reduce the likelihood of predation. Reduction of activity may also facilitate development of fever by reducing increased radiating or convective heat loss otherwise occurring when body surface is more freely exposed to cool ambience or air movement, respectively (1). In addition, at least the first phase of acute fever is accompanied or even facilitated by immobility necessary to take up a ball-like bodily posture observed repeatedly in freely moving animals aiming to further reduce body surface area exposed to a thermoneutral or cool environment. In cases of rapid rises of body core temperature the chill-phase may be characterized by the apperance of shivering, an involuntary high-frequency activity of extensive areas of skeletal muscle preventing purposeful and coordinated muscle activity needed for locomotion.

Another component of sickness behavior relevant to thermoregulation is sleep or at least increased sleepiness experienced by febrile patients during steady-state or prolonged fever after the chill-phase - if observed at all - is over. On the one hand, sleepiness may be regarded as a precondition of decreased motility (stressed and vigile animals may move around more regularly thus making them less able to save energy), on the other hand, sleepiness or even a more or less expressed depressive state experienced during most disease states could be the result of weakness, loss of appetite and thus energy deficiency. According to most theories on the function of sleep energy conservation, restoration or recovery could occur more readily during the relaxed state of body and mind characteristic of physiological sleep. Furthermore, sufficient length and balanced occurrence of various sleep states are also important. Mutual relationship between sleep and thermoregulation, i.e. decreases of core temperature during slow wave sleep representing most of sleeping time in normal persons, on the one hand, and an increased feeling of sleepiness on heat exposure, on the other hand, is compatible with the idea that high core temperature and increased propensity of sleep may be regulated in parallel.

While cellular and molecular mechanisms of non-thermal parameters of sickness behavior have been

unravelled in depth, in the majority of these studies thermoregulatory aspects have not been followed regularly or in many cases they were neglected. The present review will concentrate on possible connections between thermoregulatory changes – fever or central hypothermia – and non-thermal symptoms of sickness behavior investigated either in animal experiments or observed in human studies in the hope to understand relevant pathophysiological mechanisms. Dynamics of changes in symptoms of sickness behavior observed even during acute disease states or under stable experimental conditions presents additional difficulties in formulating simple rules of regulation especially when not only quantitative differences but also qualitative variations of thermal state of the body – hyperthermia/fever or hypothermia – can occur during the same experimental procedure.

4. ENDOTOXIN-INDUCED FEVER

In semi-restrained rats an intravenous (i.v.) injection of endotoxin (lipopolysaccharide, LPS) induces monophasic or biphasic fever of short latency and duration, if a moderate dose is given and when ambient temperature is not extremely cold or hot (9, 10). Increase in core temperature after an LPS challenge is accompanied by rises in heat production and/or tail skin vasoconstriction, a coordinated peripheral thermoregulatory effector response indicating the regulatory nature of that hyperthermia. When administered intraperitoneally (i.p.) LPS induces fever of longer latency and duration in unrestrained rats and mice; in this case a depression of locomotor activity can also be recorded (3, 11) representing one of the symptoms of sickness behavior.

Components of sickness behavior other than decreased activity were followed during LPS-induced fever using various experimental paradigms. For example, in rats anorexia or decreased food intake was observed after fever inducing dose of i.p. injection of LPS, but these two effects were uncorrelated temporally. On the one hand, while fever developed ahead of anorexia (12, 13), the antipyretic peptide, melanocortin suppressed fever, food intake and activity but, surprisingly, inhibiton of melanocortin action increased fever without affecting food intake or locomotion (13). Dissociation of temperature changes and anorexia was even more pronounced when these parameters were observed during a long term inflammatory response such as experimental colitis in the same species, in this case body core temperature remained normal in spite of the presence of general inflammation.

The central origin of fever and other aspects of sickness behavior have raised the possibility that they may be conditioned thus could be utilized in experimental and clinical applications. In rats LPS used as an unconditioned stimulus and paired with a novel-tasting saccharine solution, a conditioned febrile response was observed. Sleep, another component of sickness behavior induced by LPS could not be conditioned simultaneously (14). The same authors using a similar paradigm but observing anorexia as a conditioned stimulus found that decreased food intake could be conditioned to LPS injection (15). It seems therefore that various parameters of sickness behavior might be parts of a multifactorial host response to LPS or infection.

Anorexia, sleepiness and decreased activity belong to the symptomatology of depression, a human behavioral syndrome. Possible effects of chronic anti-depressant treatment of rats with sickness behavior induced by LPS or interleukin 1-beta (IL-1beta) was studied very recently. The antidepressant tianeptine was indeed able to attenuate several parameters of sickness behavior such as decreased social exploration, immobility and anorexia but only when LPS or the cytokine was administered peripherally (16). In addition to providing further explanation to the mechanism of action of antidepressant drugs, these data support the idea that the centrally coordinated sickness behavior could be significantly influenced by peripherally acting immune mechanisms.

Differential effect of LPS or other exogenous pyrogens on body temperature and some aspects of sickness behavior has also been found in another rodent, the mouse. In that species high i.p doses of LPS induce an acute hypothermia followed by a fever, the latter lasting for a day or so, while decreased activity can be observed much longer (11). On LPS-injection decreases in food and water intake show similar time-course with that of fever, while body mass remains low for several days after pyrogen challenge (17). Mice injected subcutaneously (s.c.) with turpentine show a large monophasic fever lasting for about a day together with an almost complete immobility (17). Dietary n-3 fatty acid added to food of these mice attenuated all measured aspects of sickness behavior in turpentine-injected mice, while in LPS-injected mice anorexia and decreased activity remained unchanged together with an inhibition of fever. It was speculated by these authors that differential action on various symptoms of sickness behavior during general inflammation (LPS-injection) may be connected to differential changes of prostaglandin E_2 (PGE_2) as opposed to the case of local inflammation (s.c. injection of turpentine) the latter affecting all aspects of sickness behavior in the same way (17). LPS-induced anorexia was also studied in mice lacking either leptin or the leptin receptor; there seems to be no absolute need for leptin for the development of anorexia, although the presence of leptin mechanisms may augment the extent of anorexia induced by the exogenous pyrogen LPS (18). Other types of exogenous pyrogens such as influenza virus (19) or a gram positive bacteria (20, 21) were also used to induce changes of body core temperature and behavioral signs of disease; mice show a large array of sickness behavioral symptoms after inoculation with influenza virus, but it is hypothermia rather than fever that could be observed (19). Rats injected intracerebroventricularly (i.c.v.) with *Mycoplasma fermentans* were observed to develop mild fever together with decreased social exploration, grooming behavior and food intake that were parallel with increased CNS production of PGE_2 (20).

An increase in sleep propensity as one of the most prominent signs of disease has been know for a long

time, in fact, the possible role of sleep as a host defense during infections was proposed more than two decades ago (22). Endotoxin and lipid-A were shown to elicit - together with fever - an increase in slow-wave sleep in rabbits (23). When these animals were infected with pathogens, the duration of enhanced sleep was shown to be positively correlated with favorable prognosis, while sleep deprivation resulted in reduced survival (24). The effects of endotoxin on human sleep and other components of sickness behavior were reported, in which marked simultaneous rises of body core temperature, slow-wave sleep duration and cytokine concentrations (TNF-alpha, IL-6) were found together with indices of increased stress activation (25). In another study carried out in humans rises in slow-wave sleep intensity and increases in cytokine levels (TNF-alpha and IL-6), thermoregulatory (fever) and circulatory parameters (heart rate) proved to be dose-dependent (26). In rats LPS-induced fever, decreased locomotion and food/water-intake is independent of the time of the day the injections were made. Except for some qualitative differences, even sleep parameters were influenced in a similar fashion: that is, decreases in REM periods and increases in slow-wave sleep intensity were observed indicating a common efferent mechanism influencing all measured parameters of sickness behavior (27).

As a summary on the characteristics of fever and sickness behavior induced experimentally by LPS it is concluded that although exogenous pyrogens represent the first factor in the chain of fever genesis, full range of sickness behavior symptoms cannot be observed or at least have not been followed in any species so far, so that there is no evidence in favor or against the parallel activation of all main components of sickness behavior under such conditions.

5. CYTOKINE-INDUCED FEVERS

Most, if not all, effects of LPS have been known to be mediated by cytokines (see 28, 29). Comparison of fever and some other components of sickness behavior in animals challenged with cytokines known to act as endogenous pyrogens have been published. Even when the same species is used, the way cytokines may effect core temperature, on the one hand, or different aspects of sickness behavior, on the other hand, may depend on the cytokine administered, the route of injection and on the receptor(s) affected. In the rat, IL-1 induces fever, decreased social behavior and food intake whether given centrally or peripherally, but fever and increased metabolic rate could be inhibited by an IL-1 receptor antagonist (IL-1ra), when both cytokines were given peripherally. As for the behavioral parameters mentioned, the blocking effect of IL-1ra was more general and depended less on the route of cytokine-administration (30). Heterogeneity of receptor mechanisms functioning during IL-1-induced sickness behavior was supported by the finding that a fall of body temperature could not be modified by IL-1ra even when both cytokines were administered peripherally, while decreased social behavior remained sensitive to the blocking effect of the antagonist (31). Another cytokine, IL-6 infused intrahypothalamically in the same species induces fever (32), but other aspects of sickness behavior such as immobility and decreased social behavior may require induction of another IL-6 receptor (33).

There is a controversy on the possible role TNFalpha, another inflammatory cytokine in fever and sickness behavior. Since its identification as one of the inflammatory cytokines (for a review see 34) playing a part in anorexia (cachexia) of chronic inflammatory diseases, a thermoregulatory effect (that is hypothermia) was also observed in different species. Later it was found that TNFalpha share rather a febrile effect with IL-1 when the former is administered in a small dose. In fact, together with IL-6, these three cytokines have been established as members of the most basic group of proinflammatory cytokines released by macrophages on LPS challenge and also possessing the capability to induces some of the behavioral effects of diseases. This clear picture has become somewhat blurred by the finding that when given in very small doses, TNFalpha may act as an antipyretic (cryogen) and by inhibiting the action of TNFalpha LPS fever may be enhanced (35, 36). Later studies, using mice deficient in one or more inflammatory cytokines, have supported the notion that depending on the dose given TNF alpha may or may not be pyrogenic, but both IL-1 and IL-6 has a role of endogenous pyrogen in rodents (37). As for the common or divergent effects of these cytokines on fever and/or other components of sickness behavior, the picture is far from being clear even when results obtained from experiments carried out on one species are considered as a paradigm. When small doses are used, the most marked effect of IL-1beta is on food intake, while IL-6 seems to be essential to fever genesis (for review see 38).

A large body of evidence has been available for cytokine-induced changes in vigilance, the decrease of which (sleepiness) is a component of sickness behavior both in animal and man. A detailed analysis of the role of cytokines in sleep regulation has been done in rabbits. In addition to LPS-induced sleep and fever (23), effects of cytokines such as IL-1, interferons and TNF and some of their receptors on fever and sleep were also studied. In particular, not only IL-1-induced fever and sleep could be blocked by IL-1ra (39), but also those induced by muramyl dipeptide (40). Both fever and sleep induced by peripherally injected IL-1beta could be attenuated by subdiaphragmatic vagotomy (41) similar to those induced by LPS (42) indicating that at least these two components of sickness behavior might develop through a nervous input to CNS sites involved in regulation of autonomic functions. To further delineate the mechanism of action of cytokines it was shown that there was a mutual relationship between IL-1 and growth hormone-releasing hormone (GHRH) culminating in GH-release (43). To elucidate the possible role of TNF in sleep and fever, a TNF inhibitor was used and proved to be effective in inhibiting IL-1 induced sleep but fever remained unchanged (44). Interferons (IFNs) are probably also implicated in sleep regulation in rabbits, since IFNalpha (but not IFNbeta) proved to be intrinsically somnogenic and pyrogenic when given in small doses (45). IFNgamma also induces fever and slow wave sleep and

may have a synergistic effect with endogenous TNFalpha in the brain (46).

Several components of sickness behavior (e.g. inactivity, anorexia, social withdrawal, fatigue, cognitive disturbances) can be observed in their complexity in patients with major depression. Very recently the idea was raised that these individuals may also present with elevated levels of plasma cytokines and their soluble receptors (47). In fact, effective treatment of patients suffering from depression may lead to attnuation of behavioral effects of cytokine (for a review see 48). In a double-blind crossover study made on healthy individuals an injection of LPS resulted in slight fever and the appearence of some symptoms of anxiety, negative emotions and memory disfunction together with rises of plasma levels of cytokines such as TNF, IL-6 and IL-1ra (49). These data extend the relationship between cytokines and sickness behavior to a broader persepective of clinical relevance. For a more detailed discussion of complex interactions among different cytokines, on the one hand, and various apects of sickness behavior and inflammation, on the other hand, see further reviews (50, 51). The author of the latter paper has coined the term „inflammatory reflex" to summarize afferent and efferent arches of cytokine-induced behavioral changes that may af-fect practically all functions of the sick body.

On the basis of the foregoing discussion it can be concluded that no clear picture has emerged as yet as to the role of major pyrogenic cytokines for their ability to mediate one or more components of sickness behavior. It seems likely that depending on the dose given and/or species applied contribution of cytokines in development of sickness syndrome may vary significantly.

6. MEDIATORS OF SICKNESS BEHAVIOR OTHER THAN CYTOKINES

As discussed briefly above, sickness behavior may be induced by LPS or other exogenous pyrogens and, in turn, by the effects of various cytokines released by macrophages or other cells of the body. Be it either a humoral input or that via the afferent vagus, release of further mediators within the CNS could be envisaged. In fact, fever and/or some components of sickness behavior have been followed as influenced by centrally acting hormones or other substances thought to act as endogenous mediators of fever and/or components of sickness behavior. Among the neuropeptides GHRH (43), cholecysokinin octapeptide (CCK-8) (52), substance P (SP) (53), neuropeptide Y (NPY) (54) have been shown to induce fever, but indices of sickness behavior have been followed only in a small number of cases. A detailed study of sleep behavior in rabbits has been carried out and GHRH was found to be a common mediator of fever and sleep (43). As for CCK-8 first it was believed that this peptide may have a role in inducing sleep and hypothermia (55). Later evidence has been collected that parallel to a coordinated rise in core temperature (i.e. fever) mediated by the CCK-B receptors (52) there was also a decrease in physical activity in unrestrained rats when CCK-8 was infused i.c.v. (cited in 56). Another parameter of sickness behavior, anorexia, seems however to be unrelated to CCK receptors in another rodent, the mouse (57).

The well established final central mediator, PGE_2 induces fever and decreased activity when infused i.c.v. in the rat (for review see 58) but decreased food intake or somnolence on LPS injection appears to be mediated without the contribution of central PGE in the chicken (59). Similarly, the finding that subdiaphragmatic vagotomy fails to influence fever in rats induced by i.c.v. injection of PGE_2 (60) supports the concept that fever and some behavioral components of sickness may be regulated at different levels (see also 7).

Effects of some centrally acting neuropeptides on fever and/or sickness behavior may also be inhibitory. For instance, corticotropin-releasing hormone (CRH) has been shown to induce increased physical activity but, surprisingly, also fever when infused i.c.v. to rats, LPS-induced fever was, however, attenuated by i.c.v. infused CRH (61). A more general inhibition of LPS-induced behavior was observed in mice when the animals were pretreated with insulin-like growth factor 1, although in this study body temperature was not recorded (62). Among the other hormones playing role in energy regulation, fever-modifying effect of melatonin and leptin was studied in some detail. In particular, in Siberian hamsters melatonin was able to attenuate fever, which effect was independent of body weight reduction developing under these circumstances (63). In rats it was shown that the febrile and anorexic effects of leptin were mediated by the established febrile cytokine, IL-1 (64). As opposed to these results, in rats lacking functioning leptin-receptor fever genesis and sickness behavior, remained undisturbed (64).

On the basis of limited information available on the relationship between central neuropeptide mediators and the energy regulation - including that relevant to fever genesis – it is difficult to draw any specific conclusion as to the necessity of neuropeptide mechanism in the development of sickness behavior or any components of it. Decreased general activity in rats on central infusion of CCK-8 (56) is in need of confirmation in other species. Even the observation of a similar phenomenon on central infusion of PGE_1 has to be complemented by looking for changes in other components of sickness behavior.

7. CNS MECHANISMS OF SICKNESS BEHAVIOR

All components of sickness behavior whether occurring one by one or in various combinations are results of efferent neural or neurohumoral pathways. Consequently, appropriate CNS mechanisms such as local release of cytokines, presence of their receptors in neurons and/or glial cells have to be available that could be induced by stimuli discussed above as possible mediators of sickness behavior. Indeed, LPS was successfully used in several studies to induce the appearance of IL-1 in microglial cells (65) and in human astroglioma cells (66). In other studies mRNA for IL-6 (67) and for IL-1beta or TNF alpha (68) could be induced in the brain of rats and of

mice. Expression of mRNA for IL-1, TNFalpha (69) or all of these three classical immune mediator cytokines (70) could be induced in the brain of mice challenged with LPS or immunized by heat-killed bacteria. Further evidence for the central mechanism of action by cytokines in sickness behavior was found when mRNA for receptors of IL-6 (67) and of IL-1beta (71, 72) could be expressed in rat and mouse brain. In turn, central injection of Il-6 in conscious rats were shown to mediate neuroendocrine stimulations, such as CRF release when applied in or around the circumventricular organs (73).

Unfortunately, in the majority of papers just cited parameters of sickness behavior were not followed, but more or less exact localization of cytokines and/or cytokine receptors within the CNS were identified (such as several hypothalamic areas and the hippocampus). Correlation of cytokine induction with behavioral changes during an immune challenge was followed in one study carried out in rats; in particular, the HIV-1 glycoprotein120 proved to be effective in inducing brain IL-1beta and TNFalpha while food intake, body mass and general activity were all decreased (74).

In addition to identifying cytokine- or cytokine receptor-transcripts in the brain of animals challenged with immune stimuli, there has been also some interest to look for more general signs of activation in CNS during fever response. For one thing, metabolic activation of hypothalamic areas thought to play a role in body temperature control has been observed in the rat at times of increased body temperature induced by injection of an endogenous pyrogen (75). Peripheral injection of LPS induced fever mediated by IL-1 that could be attenuated by an IL-ra only when the latter was administered into a circumscribed hypothalamic area indicating a high specificity of central febrile mechanism mediated by IL-1 (76). In another study the hypothalamic area - as measured by Fos activation and retrograde labeling - needed for fever response induced by peripheral injection of LPS was found to be significant (some 100 neurons), while the efferent spinal pathway proved to be even more widespread (77). In the only detailed study in which both analysis of brain activation and of some sickness behavioral symptoms were carried out during immune challenge, Fos expression was analyzed in rats with or without subdiaphragmatic vagotomy (78). After injection of LPS or IL-1 behavioral depression occurred only when the vagus remained intact; at the same time Fos expression in limbic structures and in the anterior hypothalamus could be observed together with fever. Vagotomy inhibited behavioral depression but failed to affect fever; here no Fos activation could be observed in the hypothalamic sites other than the organum vasculosum laminae terminalis. The latter area, an important site of leaky blood-brain-barrier (4) could have been reached by higher doses circulating endogenous pyrogens.

8. ”CENTRAL” HYPOTHERMIA

Relevance of hypothermia - either a „regulated” or an accidental decrease of core temperature - as a component of sickness has been known for a long time (for a review see 79), although this type of deviation of deep body temperature is a syndrome on its own, too. Even when the word ”sickness” is used in a somewhat restricted sense of an illness caused by the effects of mediators discussed in the preceding part of this review, hypothermia may occur in most severe cases of general inflammation, in sepsis. Sepsis in humans may indeed be by characterized either by fever or hypothermia (80) and in rats injected with high doses of LPS hypothermia may be observed either shortly after LPS challenge (81) or at the later phase of experimental sickness syndrome (10). The latter report gives evidence for a continuum of changes in body temperature starting with a hypermetabolic state with fever and pain under any thermal conditions which is than followed by a gradual reversal into a more passive, hypometabolic state, the latter allowing hypo- or hyperthermia depending on the thermal conditions of the environment. In other words, this later phase of „fever” may be characterized by a broad-band control of thermoregulation (82) with other components of sickness behavior (inactivity, anorexia, sleepiness, etc.) remaining largely the same.

A more or less marked lability of thermoregulation may be accounted for by an inability to increased heat production on cold exposure, widening of the so-called interthreshold zone of regulation (i. e. between core temperature threshold for increased heat loss and that for shivering). Interpretation of a fall in body temperature during severe illness ranges from an inability of central or peripheral thermoregulatory mechanisms to insure homeothermy, on the one hand, to a coordinated set of physiological changes leading to a lower set-point, hence to a „central” or regulated hypothermia. The latter interpretation envisages some purpose or biological logic that may serve survival of the sick individual. This opinion has been supported by the finding that rodents made hypothermic by hypoxia or various toxins may prefer lower ambient temperatures when the choice is given to them to seek an optimal thermal environment (83, 84, 85). As for the likely mechanism of hypothermia in animals injected with LPS the only study published so far indicates also a parallel change of selected ambient temperature and core temperature (81). Possible relationship between LPS-induced hypothermia and sickness behavior has not been studied in detail with one exception. In particular, body temperature, activity, food- and water-intake were followed in rats after an i.p. injection of high dose of LPS (86). A pretreatment with a TNF-binding protein led to an enhancement of LPS-fever, while the decrease in food- and water-intake was abolished. Interestingly, the initial hypothermia - indicating a shock-like state - and the fall in general activity remained unchanged after the inhibition of TNF-effect. These data support the notion that TNF may be regarded as a cryogenic mediator and demonstrate that various components of sickness behavior and the two phases of body temperature change (hyper- or hypothermia) may have partly different mediation, the nature of which are far from being clear.

Central or regulated hypothermia – sometimes called also anapyrexia when the phenomenon is supposed to act as an antipyretic mechanism – was observed under

conditions which may also be present during disease states. Among others, hypoxia could be a pathophysiological state that may also accompany some diseases affecting circulation, respiration or metabolism. In fact, hypoxia induces hypothermia together with a decreased motor activity in rats and may disturb circadian changes of these two parameters differently (87). As for the mechanism of hypoxic hypothermia several mediators have been suggested such as nitric oxide (88) but not vasopressin (89), lactate known to be connected to tissue hypoxia acting as a metabolic inhibitor doses apparently not mediating this anapyrexic response, either (90). Another factor likely contributing to metabolic derangements in various disease states is hypoglycemia (91). According to recent studies the hem-oxigenase product, carbon monoxide may have a role in hypothermia of hypoglycemia induced by insulin in rats (92). The lack of information on changes in other aspects of sickness behavior does not allow any conclusions to be made on possible causal relationship between regulated hypothermia and symptoms of diseases affecting energy regulation. A very recent review on hypothermia and systemic inflammation should be consulted for further details (93).

9. PERSPECTIVES

The present discussion dealt with salient features of thermoregulation as they may result in or accompanied by components of sickness behavior. Fever or hypothermia occurring in any phase of a disease have specific metabolic accompaniments (increased or decreased metabolic rates, respectively) that are needed for heat conservation or heat loss. Conversely components of sickness behavior such as anorexia, decreased motor activity and sleepiness possess strong energetic consequencies and, hence, may modify the thermal state (temperature) and energy content (body mass) of the body. The nature of relationships among these factors characterizing physiological and pathophysiological conditions are far from being understood, still some relevant information has started to emerge as demonstrated in this review.

As a further step in our knowledge it would be interesting to know if and how induced changes in any of the components of sickness behavior might influence other components and/or some thermal responses of the body. In one of these type of studies body energy state was manipulated while observing changes in sickness behavior in rats. Anorexia, weight loss and hypermetabolism was higher in animals with high body mass than in those with reduced body mass following the same stimulus, in the latter case food intake remained the same on an the immune challenge. Rats with reduced body mass developed fever and IL-6 release in the same way as those with normal or increased body mass (94). These results indicate that the inflammatory response is significantly adjusted to the actual energy status of the body while some components of sickness behavior appear to be uniform independent of the actual body mass.

The importance of sleepiness and social withdrawal as integral parts of sickness syndrome is underlined by the result of another study; in particular, sustained sleep deprivation in rats severely impaired host defence (i.e. appearance of viable bacteria the blood, hypothermia, decrease in food intake and weight loss occurred), and a shock-like state could be observed (95). It would also be logical that increased physical activity (acute or chronic exercise) could adversely affect the immune status of animals and man, if inactivity is an integral part of sickness behavior. In fact, the issue is very complex, since moderate exercise induces release of different cytokines but training may or may not influence resistance to infections (for review see 96). Manifestations of sickness behavior accompanying various disease states have thermoregulatory components in the form of fever and/or hypothermia discussed in the present review. Further investigations are needed for the elucidation of theoretical and practical aspects of mutual connection among these symptoms in the hope that modification of one or more of these symptoms may serve the benefit of patients.

Some of the controversy around the uniformity or heterogeneity of sickness behavior and its mediation discussed in the present review may be resolved if the dynamic course of that phenomenon could be divided into successive periods possessing different characteristics. A study has been just published along these lines (97) and distinguished at least two phases of the sickness behavior (called sickness syndrome). In particular, the first phase was identified as one mediated from the periphery by neural afferents and by blood-borne PGE_2; this phase was accompanied by an excitation together with the chill-phase of fever. The second (or possibly also a third) phase of sickness syndrome could be based more on endocrine afferentation and characterized by anabolic components such as inactivity or sleepiness. This intriguing hypothesis could allow fresh insight into the dynamics and complex nature of sickness behavior as it is know today.

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