Sickness Behaviour: Causes and Effects

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Abstract

This paper discusses sickness behaviour as a central motivational state. It deals with the adaptational value and underlying mechanisms of sickness behaviour and with the consequences of the body's failure to terminate the activity of the symptoms-producing cytokines. ***(SA Fam Pract 2003;45(9): 15-18)***

INTRODUCTION

Sickness behaviour is defined as the coordinated set of behavioural changes that develop during infection. These behavioural changes include fever, somnolence, loss of libido, decreased locomotor activity, loss of appetite, disinterest in the social and physical environment and general anhedonia.[1,2] Sickness behaviour is not a sickness-induced debilitation, but rather a new physical and mental homeostasis meant to enable the individual to best counteract the infection. This functional homeostatic adaptation is the effect of pro-inflammatory cytokines on the brain and is controlled through neurohormonal mechanisms.[1] In this paper, we shortly discuss the adaptational value and then the underlying mechanisms of sickness behaviour.

ADAPTATIONAL VALUE OF SICKNESS BEHAVIOUR

Sickness behaviour is the reorganisation of behavioural activities in response to disease. The following paragraphs discuss the usefulness of fever, somnolence, loss of libido and appetite, decreased locomotor activity and anhedonia in response to an infection.

Several arguments favour fever as an essential component of the host response to infection, including a) the argument that it is unlikely that a process as costly in terms of energy expenditure would have persisted throughout evolution if it did not have a function, b) the results of many studies that show that fever during bacterial infections is associated with a better prognosis, c) the increase in morbidity and mortality in animal studies on the use of antipyretics to attenuate fever, d) experimental evidence which shows an adaptive function for hyperthermia and e) the highly regulated nature of fever which implicates that fever must have developed as a host defence mechanism.[3] Fever is further known to play a role in the suppression of microbial growth in an iron-deficient environment. It is also known to stimulate processes such as the expression of adhesion molecules that enhance leukocyte migration, the proliferation of T cells, the bactericidal activity of neutrophils and the pro-inflammatory cytokine profile.[3,4,5] In addition, it is said to protect against the infection-induced disturbance of membrane lipids by phospholipase and, by so doing, to protect the integrity of membranes with regard to signal transduction and receptor expression.[6]

Numerous studies have shown that sleep deprivation has a negative effect on immunity. However, the value of somnolence, another well-recognised characteristic of infectious diseases, is generally accepted, although poorly investigated. One of the very few studies on the positive effects of excessive sleep show increased non-REM sleep to be positively correlated with survival.[7]

Loss of appetite and libido are said to reduce the intake of nutrients (especially iron) that are necessary for the proliferation of the pathogen, and to prevent conception in the sick female individual – a risk factor for abortion and abnormal development.[8]

The decreased locomotor activity and anhedonia found in sickness behaviour are reminiscent of the symptoms of depression. This is not surprising, as a cytokine profile similar to that of sickness behaviour has been reported for major depression. Similarities in sickness behaviour and depression include fatigue, psychomotor slowing, anorexia, lethargy, a decrease in certain cognitive abilities, such as thinking and concentration, as well as low interest in socialising and reproduction. The adaptive advantage of cytokine-induced depression during infectious disorders probably lies in the fact that it forces the individual not to become involved in activities that will test his or her coping abilities, to slow down and to conserve energy expenditure for the adaptive febrile response and immunological activity.[8,9]

UNDERLYING MECHANISMS OF SICKNESS BEHAVIOUR

Sickness behaviour is initiated by pro-inflammatory cytokines produced by activated monocytes and macrophages in response to infections. These

cytokines can either influence cerebral activity directly, or induce up-regulation of cerebral cytokine production.[1] In addition, gram-negative bacteria-derived lipopolysaccharides (LPS) can stimulate the process by binding to the CD14 receptor on these mononuclear phagocytes. Interestingly, cytokine-induced sickness behaviour can also develop in many non-infectious general medical conditions, e.g. in some cases of chronic inflammatory and auto-immune diseases and neurodegenerative conditions, and post-partum.[8]

The major pro-inflammatory cytokines involved in sickness behaviour are interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor a (TNFα),[10] with IL-1 being viewed as the prototypical pro-inflammatory cytokine.11 T cell-derived interleukin-2 (IL-2) might also be involved. The role of the IL-1 family, i.e. IL-1α, IL-1β, the receptor antagonist cytokine IL-1ra and the receptors involved in sickness behaviour, is somewhat complex and will not be discussed in detail. Suffice to say that IL-1β is produced as a precursor, that several factors are involved in controlling its conversion to the active IL-1β and in controlling the latter's activity at the receptor level. At the receptor level, the actions of IL-1 are regulated by a type I IL-1 receptor, which (via nuclear transcription factor NFκB) functions as the signal transducer, while a type II IL-1 receptor down-regulates IL-1 actions by acting as a decoy receptor in binding excess IL-1. Receptor activation can further be down-regulated by the receptor antagonist cytokine IL-lra, which prevents signal transduction.[1]

Cytokines, which are produced by peripheral immune cells, can signal the brain to up-regulate cerebral cytokine synthesis and release. This would augment the effects of the peripherally-derived cytokines.[1] There are various routes through which peripherally-derived cytokines can influence neural function and it is postulated that different routes predominate under different conditions.[12] The pathways through which cytokines signal the central nervous system, and thus behaviour, include: a) blood-borne mechanisms by which cytokines are transported from the area of secretion to the brain and b) neural mechanisms by which cytokines influence peripheral nerves, which in turn transfer the information to the appropriate cerebral structures. Signalling through the circulatory transport of cytokines, i.e. blood-borne mechanisms, includes:

- Cytokine carrier mechanisms. Saturable cytokine carrier-mediated mechanisms can transport cytokines across the concentration gradient to the brain and are responsible for at least a small amount of the signalling.[13,14]
- Entry of cytokines at the circum-ventricular organs (CVOs).[13,15] These are areas devoid of the blood-brain barrier and include the area postrema and the organum vasculosum of the lamina terminalis. Entry through these areas does not, however, provide entry to the rest of the brain, i.e. areas where cytokine effects are known to take place. It is thought that cytokines bind to cytokine receptors on the CVO – an event that stimulates prostaglandin synthesis. Prostaglandins, which are highly lipophilic, are able to cross the blood-brain barrier and reach cerebral areas that are not directly accessible to cytokines. Prostaglandins can then activate the neurons that project to the paraventricular nucleus and other structures of the hypothalamo-pituitary-adrenocortical (HPA) axis, as well as to the amygdala and central noradrenergic neurons (CNA).[15,16,17]
- Binding of cytokines to cytokine receptors on cerebral blood vessels with subsequent signal transduction. The process is very similar to that of binding to receptors on the CVOs. Cytokine binding to these receptors on the vasculature can, as before, lead to prostaglandin synthesis, resulting in neuronal activation and projection to the appropriate cerebral controlling areas.[13,18]

Signalling occurs through effects on the peripheral nerves, amongst others through vagal afferents. Immune cell-derived cytokines such as IL-1 act locally, in a paracrine fashion, to stimulate vagal afferents, which would then signal the appropriate cerebral areas.[13]

The intracerebral effects of pro-inflammatory cytokines can directly and indirectly cause all symptoms of sickness behaviour. The direct mechanisms involve alteration of the basal activity of neurohormonal systems, such as the hypothalamo-pituitary-adrenocortical (HPA) axis, the central noradrenergic (CNA) system and the central serotonergic systems.[19] Indirect mechanisms involve the activation of intermediates such, as prostaglandin synthesis and NO release through intracerebral cytokine-induced cyclo-oxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) activation. These intermediates are implicated in the alteration of neural pathways involved in somnolence and fever, as well as in those involved in behavioural effects that are mediated through the activation of the central corticotrophin-releasing hormone (CRH) and the HPA-axis, e.g. anhedonia, loss of libido and anorexia.[1,20,21,22] For more detailed information on the contribution of specific cytokines to the individual components of sickness behaviour, the reader is referred to the overview by Dantzer *et* al.,1999.[23]

It is very important that the infection-induced synthesis and activity of pro-inflammatory cytokines is strictly controlled and limited to the period of the disease. Several substances are involved in the control of pro-inflammatory activity, including the anti-inflammatory cytokines, glucocorticosteroids, ADH, α-melanocyte-stimulating hormone and members of the interleukin-1 family.[1,2,24,25,26,27] The molecular mechanisms involved in the containment of the sickness response are sometimes referred to as the cryogens.[24] As has been mentioned previously, the HPA-axis is stimulated by pro-inflammatory cytokines. The glucocorticoids secreted in this manner can, in turn, control the cytokine-induced effects by a) down-regulation of pro-inflammatory cytokine synthesis and release through inhibition of the transcriptional and posttranscriptional expression of the IL-1β gene and

decreasing the stability of the IL-1β mRNA, b) decreasing the ratio of type I IL-1 to type II IL-1 receptors, and c) suppressing the conversion of proIL-1β to its biological active form through inhibition of the IL-1b-converting enzyme.[1,26,27] Fever-induced ADH has further been shown to limit the suppressive effect of IL-1β on the behavioural functions.[25] The failure of any one of the factors involved in terminating the inflammatory process can contribute to the continuation of the sickness behaviour. An interesting phenomenon is that the pro-inflammatory cytokines themselves can contribute to the continuation by inducing glucocorticoid resistance. IL-1α, for instance, was shown to suppress glucocorticoid translocation and glucocorticoid-mediated gene transcription[28] and, in so doing, to inhibit the negative feedback on the production of pro-inflammatory cytokines.

Failure to limit sickness-induced cytokine production can have serious long- and short-term effects. The effects of immediate, severe, uncontrolled activity on multiple organ functionality are well-known, e.g. septic shock, systemic inflammatory syndrome and multiple organ failure. However, mild to moderately increased pro-inflammatory cytokine activity after recuperation from the infectious condition can lead to cognitive, emotional and physical symptoms that impair the quality of life. Cognitive and emotional effects include inability to concentrate, irritability, bad temper, anhedonia, apathy, and even anxiety and depression, while physical signs include symptoms such as fatigue, headaches, swollen lymph nodes and sore throat.[8,29] This prolonged continuation of the symptoms of sickness behaviour has even been implicated in post-viral fatigue and chronic fatigue syndromes.[8,30] The symptoms of sickness behaviour may very well underlie some of the neurobehavioral changes that are responsible for poor patient compliance.

There are indications that some antidepressant drugs may be successful in the treatment of cytokine-induced depression.[8,28] Whether this is mediated through a suppression of the induction of pro-inflammatory cytokines by activated immune cells, glial cells or neurons, or through their effects on the cytokine-induced changes in the neurohormonal activity, is, in many cases, still under investigation.

Sickness behaviour has been described as a central motivational state with the selection of appropriate strategies to counteract the disease.[1,31] There is ample evidence to show that, if any other factor is perceived to be of more importance than the disease, it would override the sickness behaviour, e.g. the fear motivational state may take precedence over the sickness behaviour motivational state and behaviour would be aimed at counteracting whatever elicited the fear.[1,31,32] The underlying mechanisms involve psychologically-induced neurohormonal activation overriding cytokine-induced neurohormonal activation. Most medical practitioners could probably attest to extreme fear or pleasure overriding the characteristic behaviours of sickness.

CONCLUSION

In summary, it can be said that sickness behaviour is a functional homeostatic adaptation caused by the induction of pro-inflammatory cytokine production, rather than a debilitating side effect of infectious diseases. However, if this pro-inflammatory activity is not terminated after recuperation from the infectious condition, it may lead to low-grade emotional, cognitive and physical problems that can impair the quality of life and could possibly contribute to patient non-compliance.

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