Physical Exercise, Acupuncture and Immune Function

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Summary
Experimental evidence suggests that the immune system is influenced by various types of psychological and physiological stressors, including physical activity. Natural immunity, representing a first line of defence in viral infections and cytotoxicity to a variety of tumour cells, is strongly influenced by frequent exercise. This regulation includes interaction between the nervous, endocrine and immune systems and central mechanisms including the endogenous opioids are of great interest here. Chronic activation of endogenous opioid systems augments natural cytotoxicity, and the possible involvement of opioids in the exercise-induced enhancement of natural immunity is discussed. Few reports are available on acupuncture and its effect on immune function but, interestingly, the effects of acupuncture and physical exercise are somewhat similar. The physiological significance as well as the underlying mechanisms of the reported changes in natural cytotoxicity after exercise training and acupuncture is as yet unclear. However, moderate exercise training has been associated with elevated natural immune function and reduced upper respiratory tract infections and available epidemiological and experimental studies suggest that moderate physical exercise may protect against several forms of cancer.

Key words
Acupuncture, Endorphins, Exercise, immune function.

Introduction
It has been shown that immune function is influenced by both psychological stressors and physiological mechanisms. This includes an intricate interaction between the nervous, endocrine and immune systems, although specific pathways and mechanisms are far from, being fully understood. The conceptual basis for studying the influence of physiological stimuli on immune function originally derives from the work of Walter Cannon and Hans Selye. Cannon was the first to introduce the concept of homeostasis and the activation of the sympathetic nervous system as a first line of defence against acute disturbance stimuli. Selye introduced the syndrome that was produced by diverse nocuous stimuli and coined the term stress. He showed that diverse factors, including excessive muscular exercise, could lead to a number of hypothalamic-pituitary-adrenocortical responses that have an impact on the immune system. It is known that exercise can strongly influence the immune function. Recently, Hoffman-Goetz and Pedersen (1994) discussed the exercise-immune interaction as a subset of stress immunology, referring to the fact that acute intense exercise causes much larger changes in the concentration of circulating immune cells and hormones than psychological stress does (10).

Exercise and immune function
The earliest and best-documented effect of exercise on the host defence system is the acute leukocytosis. The first experiment on this leukocytosis was described in 1893. Since then, numerous studies on physical exercise and immune function have been published and there are experimental indications, from both human and animal studies, that exercise can influence various functions of the immune system. One of the most widely studied parameters in exercise immunology is natural killer (NK) cells. NK cells are a subpopulation of lymphocytes which are spontaneously cytotoxic to a variety of tumour cells and virus-infected cells.

The effects of acute exercise on NK cell function and number seem to vary depending on the type and intensity of exercise. Generally, there is a transient augmentation of NK cell activity during moderate as well as strenuous exercise, followed by immunosuppression after strenuous exercise only. Overall, during exercise there are more lymphocytes recruited to the blood. This recruitment is more pronounced for NK-cells compared to T-cells (22).

The basal levels of NK cell activity have been shown in some but not all studies to be elevated...
Acupuncture and immune function

The similarities between acupuncture and physical exercise have been discussed by several authors (1,28). Acupuncture excites receptors or nerve fibres in the stimulated tissue which are also physiologically activated by strong muscle contractions. Thus, some of the functional effects which have been attributed to acupuncture can also be noted during muscle exercise (1). For instance, both nerve stimulation and extended regular exercise can give a sustained reduction in blood pressure. Endogenous opioids are released both in response to exercise and acupuncture (9,28) and similar concentration of neuropeptides is seen after electro-acupuncture and exercise in the hippocampus in rats (5).

Rather few, but interesting reports are available on acupuncture and its effects on immune function. Twenty years ago, Sabolovic and Michon (1978) showed that acupuncture treatment in humans could influence both T-cells and B-cells in peripheral blood (25). The Peking symposia on acupuncture and moxibustion in 1979 contained more than 44 papers related to acupuncture and the defence system in the body; the results were discussed by Rogers and Bozzy (1981). It was concluded that stimulation of the acupuncture points by a variety of techniques had major physiological and therapeutic effects on the defence system both in animals and man. Under experimental conditions, stimulation of certain points caused leukocytosis and increased phagocytosis (24). These effects are shared with the common effects seen after physical exercise (21). Acupuncture has also been shown to suppress immune function (26).

The NK-cells, one of the most studied parameters in exercise immunology, have also been frequently studied in response to acupuncture (27). The effects on NK cell cytotoxicity seen after acupuncture is similar to that previously seen after exercise training (73). Several authors have studied plaque-forming cell (PFC) production in a response to acupuncture. While some have reported decreased PFC formation (26), others have shown an increase (8,16). Furthermore, these papers both suggest an involvement of the autonomic nervous system in the increased PFC formation. Some authors have suggested that the immune modulation seen after acupuncture may share a common nervous pathway with acupuncture analgesia-producing systems (27). One of the possible mechanisms involved in the immune-modulation shared between acupuncture and physical exercise is the endogenous opioid system (7,14,29).

Possible regulatory pathways

Which possible regulatory pathways are involved in the exercise- or acupuncture-induced augmentation of natural immunity? Neural regulation of neuroendocrine, metabolic and cardiovascular responses to exercise seems to be dependent on central nervous system mechanisms. Regarding the exercise effects, both the neural feedback from working muscles (exercise pressor reflex) and the central command mechanisms determine the activity in higher neuroendocrine centres during exercise. The afferent pathway in the exercise pressor reflex appears to be mediated by activation of slow conductance, thin, myelinated Group III or unmyelinated Group IV fibres, arising from the contracting muscles. Lesioning studies have shown that the involvement of the CNS in immune modulation points towards an integrated circuitry of the limbic system, hypothalamus and brainstem autonomic nuclei that regulates both autonomic and neuroendocrine outflow (18).

Different stressors can activate the endogenous opioids, and their influence on a wide range of biological functions has been suggested. The endogenous opioid systems are widely represented in regions which are involved in the stress response, e.g. the hypothalamus, pituitary and adrenals. There are numerous studies showing that plasma levels of B-endorphin released from the pituitary are increased by physical activity, but it is also well known that both acupuncture and exercise activate the CNS opioid system (1). Chronic regulation of natural immunity during exercise might to some extent involve central opioid receptors. Thus, central chronic administration of B-endorphin augments...
in-vivo natural immune function, and the effects are suggested to be mediated by $\delta$ or $\mu$ opioid receptors. Prolonged voluntary exercise in rats also affects CNS endorphinergic, dynorphinergic and enkephalinergic mechanisms (11,12).

There is rapidly increasing evidence, mostly derived from in-vitro studies, that opioid peptides as well as other neuropeptides can influence the immune system (19). Identification of receptors for neuropeptides and steroid hormones on cells of the immune system has created a new dimension in endocrine-immune interaction (6). Opioid peptides, and in particular B-endorphin, can modulate natural immunity such as NK cell activity and in most studies the effects could be completely or partly reversed by naloxone, indicating that an opioid receptor is involved. Accumulating evidence supports the hypothesis that the central endogenous opioid system is part of the regulatory pathway between the central nervous system and the immune system.

Studies available on the central opioid system and NK cell function dealing with acute activation of the CNS opioid systems, have consistently shown immunosuppression (2). Possibly, suppression or enhancement of natural cytotoxicity might be induced via different opioid receptors. There is also a possibility that the same receptor type could mediate different effects of opioids on the immune system in a dose dependent way.

The pathways by which the CNS may communicate with the periphery include neuroendocrine outflow via the hypothalamic-pituitary-adrenocortical axis, and the autonomic nervous system through direct nerve fibre connections with cells or the organs of the immune system. Neuroendocrine hormones mainly derived from the hypothalamus and the anterior pituitary have been suggested to be involved in immunomodulation. b-endorphin and ACTH are secreted from the anterior pituitary in response to exercise. Both these hormones have been shown to modulate NK cell activity and thus could be involved in the exercise-induced augmentation (27). Other adrenohypophyseal hormones such as CH and prolactin could be involved in the modulation of immune function in response to exercise: CH and prolactin levels are increased in response to exercise and it has been demonstrated that lymphoid cells contain receptors for these hormones.

Many authors have described a bi-directional communication between the nervous system and the immune system. Evidence for an adrenergic and peptidergic innervation of specific regions of primary and secondary lymphoid organs has established the links necessary for neural modulation of immunity. Postganglionic noradrenergic sympathetic nerve fibres are widely distributed in organs of the immune system such as the spleen and thymus.

Many authors have discussed the functional role of the autonomic nervous system in immunoregulation. Large numbers of b-adrenoeceptors, mainly of the $\beta_2$ subtype, are found on NK cells, and in-vitro studies have shown that catecholamines selectively affect adhesion of NK cells to endothelial cells (3). We have demonstrated that catecholamines are involved in the exercise-induced augmentation of in-vivo cytotoxicity in rats (15) and others have shown that the adrenergic system is involved in the acupuncture-induced augmentation of immune function (8,16,29). In exercise, the catecholamine effects, mediated by b-adrenergic receptors, could include the recruitment of NK cells from the spleen or other sites to the circulating pool, due to the reduced adhesion of NK cells to endothelial cells. Catecholamines could also directly augment the cytolytic activity of the cells.

**Conclusion**

Many of the hypothetical pathways discussed in this paper are purely speculative, and greater understanding of this intricate interaction between the nervous, endocrine and immune systems is needed.

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