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Discussion

Psychoneuroimmunology for physiotherapists

Leslie Alford*

University of East Anglia, Norwich NR4 7TJ, UK

Abstract

Physiotherapists working in musculoskeletal areas have acknowledged that they need to know more about the body than bones, muscles and joints. Over time, physiotherapists have expanded their knowledge into other areas and systems of the body. Psychology, the nervous system, physiology and biomechanics are all examples of areas that have been covered and analysed in greater depth. Understanding more of the body's systems and how they link together can help to reduce some of the mysteries that arise in clinics on a daily basis. Through scientific explanation of patient conditions and their response to treatment, the effectiveness of physiotherapy can be improved. A new field that offers to further improve physiotherapy understanding and patient management is psychoneuroimmunology. This article aims to introduce this field to physiotherapists and review recent findings on stress-impaired healing.

Keywords: Psychoneuroimmunology; Physiotherapy; Biopsychosocial; Healing

Introduction

Psychoneuroimmunology (PNI) is a relatively new field that deals with the interactions between the central nervous system (CNS), the immune system and the endocrine system [1]. It began with the clinical observation that psychological factors play a role in the aetiology and course of many conditions [2]. As research into this link progressed, many previously held assumptions were shown to be incorrect. One of these was the functional autonomy of the immune system [3]. It was discovered that many aspects of the immune system could be controlled or modulated by the brain. It was also discovered that this worked in reverse, with the immune system communicating to and altering brain processes. The end result is bidirectional communication between the brain and the immune system [4].

As research findings in PNI progress, it is playing a growing role in many areas of medicine. For a long time, these were of no direct relevance to physiotherapists. However, with the growing dominance of the biopsychosocial model and PNI findings in the areas of tissue healing and pain, this has changed. An electronic search of MEDLINE (1966 to December 2005), AMED (1985 to December 2005), EMBASE (1980 to 2005 Week 52) and CINAHL (1982 to December Week 2, 2005) using the keywords 'psychoneuroimmunology', 'PNI', 'physiotherapy' and 'physical therapy' revealed that, to date, there are no articles written on the subject for physiotherapists. This article has two primary objectives: to introduce PNI to physiotherapists by discussing some of the major concepts from this field; and to use research from the stress and healing literature to demonstrate how PNI can be of relevance to physiotherapists.

The basics

The brain is considered to have two main systems for influencing the immune system: neuroendocrine outflow via the pituitary; and through direct neuronal influence along sympathetic, parasympathetic and peptidergic fibres [3,5]. An important and well-researched component of the first system is the hypothalamic-pituitary-adrenal (HPA) axis. This system is often discussed in the stress literature. The starting point of the HPA axis is the hypothalamus, which can be activated by a variety of stimuli including thoughts and emotions [6]. The hypothalamus signals to the pituitary gland through neural and/or vascular connections. Stimulation of the anterior pituitary causes the release of propiomelanocortin, which splits to form adrenocorticotropin (ACTH) and beta endor-

* Tel.: +44 1603 596161; fax: +44 1603 593166.
E-mail address: leslie.alford@uea.ac.uk.

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phin [6]. ACTH is circulated through the bloodstream until it reaches the cortex of the adrenal gland where it stimulates the release of glucocorticoids (primarily cortisol) and mineralocorticoids (primarily aldosterone) [7,8].

The second system involves direct neural influence of lymphoid organs, blood vessels and the adrenal medulla [5]. The sympathetic-adrenal-medullary (SAM) axis is often described in the literature as a major contributor to this system. The SAM axis involves sympathetic stimulation of the adrenal medulla causing the release of catecholamine (adrenaline and noradrenaline) hormones [7]. Through the combined activation of the HPA and SAM axes plus other components, the brain is able to influence many aspects of the immune system. These include alteration of:

- the number of circulating leucocytes;
- mitogenic lymphocyte responsiveness;
- antibody production; and
- cytokine production/mix and the balance of cellular and humoral immunity [9].

The reader will recall that this is a bidirectional system and the immune system is also able to communicate with and alter functioning within the brain. Cells of the immune system communicate with each other as well as other cells within the body using messenger molecules called cytokines [10]. Research indicates that experimental alteration of cytokine levels within the bloodstream can cause a range of behavioural and biological responses that could only be mediated by the brain [10,11]. This means that the immune system is able to communicate with and alter functioning within the CNS. This finding triggered research into the mechanisms that the immune system uses to achieve this. It is now thought that both blood-borne and neural routes allow the immune system to communicate with the brain [12]. Despite the presence of the blood–brain barrier, blood-borne cytokines seem to have a number of means for getting messages either directly through or around this barrier [10]. The vagus nerve has long been established as a relay for immunological information to the brain. More recent research indicates that the glossopharyngeal nerves are also involved in a similar role [13]. Wieseler-Frank et al. [12] believe that other peripheral nerves may also be capable of relaying afferent immunological information.

What has all this got to do with physiotherapy? Kronfel and Remick [14] note that neuroscience and immunology are two of the fastest growing fields in the medical sciences. These two areas come together in PNI. Findings from this burgeoning field are making important contributions to the disciplines of psychiatry, oncology, rheumatology, occupational health and others. Through PNI research, many previously enigmatic disorders are beginning to reveal some of their secrets. PNI is also offering new therapies and approaches for many conditions [12,14–16]. For physiotherapists, PNI can help to explain many of the reasons behind the biopsychosocial assessment and treatment paradigm. With respect to psychosocial influences, a particularly well-researched area is the effect of stress on tissue healing. The remainder of this article shall discuss this relationship and outline one of the main mechanisms involved.

Tissue healing

Physiotherapists deal with many patients who have damaged tissues following surgery or traumatic injury. An important part of managing these patients is optimising the speed and quality of repair and recovery. Physiotherapists are familiar with the concept that appropriate graded movement and loading of repairing tissues is essential for full recovery [17]. Less familiar may be the deleterious effect that psychological stress can have on healing. Many studies published in the medical literature have explored this effect, and it is well established, in both animal and human trials, that stress delays the healing of superficial wounds [18–24].

Many of these studies have been performed in highly controlled laboratory trials using either rats or mice [22,24–26]. The design of these trials involves the use of standardised cutaneous wounds across control and experimental groups. A stressor, with or without other interventions, is applied to the experimental group/s. Wound healing plus a variety of physiological variables are measured. These trials have consistently shown that restraint-induced stress delays the healing of superficial wounds by 25% or more.

Findings from highly controlled laboratory research on rodents cannot automatically be assumed to hold true in humans. To address this issue, several studies have assessed the effects of stress on human wound healing. Kiecolt-Glaser et al. [19] were one of the first groups to undertake this research when they compared the healing rates of 13 female caregivers with matched controls. Long-term care giving is associated with a prolonged stress response [4,27]. Both groups in this study were given standardised punch biopsy wounds to their non-dominant forearm. The wounds were monitored until completely healed. The caregivers took, on average, 24% longer to heal; this equated to a difference of 9 days, which is a clinically significant margin. Marucha et al. [18] used a different study design to assess the effect of examination stress on oral mucosal healing in dental students. Eleven students were given standardised wounds to the hard palate. The first wound was made at the end of their summer vacation and the second wound was made 6 weeks later, just before an important examination. The healing times of wounds were monitored. They found that, on average, the pre-examination wound healed 40% more slowly than the holiday equivalent. Although there was variation among the students in the size of effect, all of the students healed more slowly during the examination period.

Both of these studies had small numbers of subjects and, unlike the animal studies, could not control for possible confounding variables such as health behaviours. However, findings from these two studies were enough to stimulate other human studies assessing the effect of stress on healing.

Ebrecht et al. [28] performed a prospective study with 24 men in which subjects completed questionnaires on perceived stress, health behaviours, personality factors and assessment of cortisol levels. Standardised cutaneous wounds were used. Data for assessment were taken 2 weeks prior to wounding and in the weeks following wounding. The most relevant results from this study were that subjects in the slow-healing group were significantly more likely to have higher perceived stress scores as well as higher morning cortisol levels on the day after wounding. This study also found that alcohol consumption, exercise, healthy eating and sleep were not correlated with healing time.

A criticism of all the studies reviewed to date is that they involved experimentally inflicted wounds and thus did not assess real patients in a clinical environment. Two studies to address this looked at the effect of psychological factors/stress on healing of leg ulcers, and wound physiology plus recovery, following surgery. The first of these, Cole-King and Harding [20], assessed the healing rates of 53 patients with chronic lower leg ulcers over a period of 3 months. Patients who took part in the study completed the Hospital Anxiety and Depression Scale. This scale is a well-validated psychometric questionnaire. The study found that higher levels of both anxiety and depression had a statistically significant association with slower healing.

Broadbent et al. [29], in their study of 47 adults undergoing surgical repair of inguinal hernia, focused on assessing the influence of psychological stress on a number of key cytokines and enzymes from the wound in the early post-surgical period. Interleukin-1 (IL-1), interleukin-6 (IL-6) and matrix metalloproteinase-9 (MMP-9) are all important in early wound repair processes. Broadbent et al. [29] assessed their patients to see if pre-operative measures of psychological stress (Perceived Stress Scale) and level of worry about the surgery (Visual Analogue Scale) were correlated with the early post-surgery levels of IL-1, IL-6 and MMP-9 from the wound. This study had a poor start, as 11 of the subjects were lost from the study immediately after surgery. The surgeon forgot to insert wound drains into eight of the subjects, one subject had a myocardial infarction, and two subjects had blocked wound drains. This meant that fluid from the wounds of these subjects was unavailable for analysis. Results from the remaining subjects indicated that high perceived stress and worry levels predict low IL-1 and MMP-9 levels, respectively. However, neither stress nor worry was correlated with IL-6 levels, and physiological variables were not associated with self-reported recovery. It was also expected that decreases in IL-1 would be associated with decreases in IL-6 and MMP-9; however, this was not found. The study did not control for smoking, which the authors recognised could be responsible for the raised levels of MMP-9. This study provides a tantalising glimpse at the possible influence of psychological factors on early healing in surgical wounds; however, mistakes and the lack of control of confounding variables mean that no conclusions can be made. It does, however, set the stage for further studies in this area.

Another interesting study in this area was conducted by Kiecolt-Glaser et al. [21]. This group recruited 42 married couples to their crossover design trial. Strict inclusion and exclusion criteria was applied to minimise the risk of confounding variables influencing the study results. The exclusion criteria included any health disorders that could alter immune and endocrine functioning, and any recent or active health problems such as cancer, diabetes, surgery, vascular problems, stroke or asthma. Couples were also excluded if either spouse smoked, took blood pressure or anti-inflammatory medication, or had an excessively high caffeine or alcohol intake. The couples were admitted to a hospital research unit on two occasions for 24-hour periods. In one session, couples participated in structured social support interaction. In the second session, conflict was deliberately encouraged through the discussion of marital and personal grievances. Standardised cutaneous wounds were used to assess the effect on healing time. Fluid from the wounds was also analysed. The study found that cytokines important in the early healing phase [IL-1, IL-6 and tumour necrosis factor (TNF)] were lower at the wound site following the conflict session. The study also found that couples who displayed more hostility across both sessions healed 60% more slowly than low-hostility couples.

These studies provide firm evidence that, in both animals and humans, psychological factors/stress can influence the healing rates of superficial wounds. Good evidence also exists that psychological factors can alter wound cytokine and enzyme levels in the early stages of healing. Less clear are all the pathways and thresholds that underlie this process. It must also be noted that these effects have primarily been observed with cutaneous wounds. Although the repair processes in many parts of the body are essentially the same, findings on cutaneous wound healing cannot automatically be assumed to be the same for all musculoskeletal tissues. These studies have also triggered associated research into other aspects of stress and wound healing, and one of the early studies found that bacterial infection rates were much higher in restraint-stressed mice [22]. There is scope for further investigation on this topic as healing and psychological factors impact across all areas of medicine.

Possible mechanisms involved

To date, the most closely examined mechanism for delayed healing is the influence of stress on early wound physiology. After a wound has occurred, the first phase of healing is inflammation. Inflammation initially involves changes in local blood flow and the accumulation of a wide range of cells including mast cells, dendritic cells, monocytes, neutrophils and lymphocytes. These play a key role in clearing the area of debris, bacteria and dead cells, and preparing the wound environment for fibroblasts and repair processes [30]. Cytokines, chemokines and lipid mediators play a key role in orchestrating many of these various processes. A group

of cytokines with a pro-inflammatory action have received much research attention and are often referred to in the literature [5]. The pro-inflammatory cytokines IL-1, IL-6, IL-8 and TNF have been shown to be present in lower levels at the wound site of stressed humans [21,23,29]. It should be noted, however, that IL-8 may also be anti-inflammatory. The role it serves depends on its concentration at the wound site [10].

The evidence is strong that psychological factors can influence cytokine levels within the circulation and locally at wound sites [9,10,21,23]. One of the ways that psychological factors can influence systems within the body is through the stress response. The stress response has evolved as an important survival mechanism; mobilising energy, redirecting blood flow to muscles and the brain, increasing blood pressure and heart rate, increasing blood coagulation and decreasing pain sensitivity [8]. These physiological responses can be very helpful when dealing with a short-term physical or mental challenge. When activated for prolonged periods of time, the physiological effects of the stress response can have numerous deleterious effects on the body [8,31,32]. In modern-day societies, the stress response is activated most frequently by perceived threats (psychological stress) rather than actual fight or flight situations [32].

The stress response can be activated by many different stimuli. The brain assesses and integrates information from a wide range of sources. Memories, thoughts, and the internal and external environment of the body can collectively or individually stimulate a stress response [6]. Two of the major arms of the stress response are the SAM axis (one of the tools of the sympathetic nervous system) and the HPA axis [8]. The activation of these axes causes the release of a wide range of steroid hormones, of which, for the immune system, cortisol and the catecholamines are the most important [9]. Lymphocytes, monocytes and granulocytes have receptors for many of these steroid hormones. Stimulation of these cells by various steroid hormones can cause changes in cellular trafficking, cytokine secretion, antibody production, and mitogenic and cytolytic activity [7]. Many of these processes are important in the early stages of wound healing, and it was noted previously that a number of studies have shown reduced pro-inflammatory cytokine levels in the wounds of stressed individuals. Although this is a well-researched route, Padgett and Glaser [7] note that PNI research is continuing to find other physiological pathways that may be involved.

Summary

PNI is a growing field within the medical sciences. As research findings from PNI have expanded, the influence of this field is being felt in many divergent areas of medicine. This article has reviewed some of the key principles and mechanisms of PNI, and discussed how this may be of relevance to patients with injured tissues. Although this article focused on this aspect, PNI has relevance for physiotherapists in many other areas. Some of these include pain, auto-immune diseases, chronic fatigue syndrome, overtraining syndrome and the biopsychosocial model [12,15,16,31–37].

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