

REVIEW ARTICLE

Psychoneuroimmunology and the Skin

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The nervous, immune, endocrine and integumentary systems are closely related and interact in a number of normal and pathological conditions. Nervous system mediators may bring about direct changes to the skin or may induce the release of immunological or hormonal mediators that cause pathological changes to the skin. This article reviews the psychological mechanisms involved in the development of skin diseases. Key words: melanocyte-stimulating hormones (MSH).

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The nervous and immune systems reciprocally regulate each other through different cross-reaction mechanisms. The link between the central nervous system (CNS) and the immune system is represented by the hypothalamic-hypophyseal-adrenal (HPA) axis, which secretes the corticotrophin releasing hormone (CRH) and the autonomous nervous system. The CNS and the immune system intercommunicate via neurotransmitters, cytokines and endocrine neurotransmitter hormones (adrenalin and corticoids). The interconnection between the two systems is complex and the interactions between them are bidirectional.

Neurons use many different chemical signals to communicate information. They release neuropeptides, neurotransmitters, cannabinoids and even some gases like nitric oxide. Neurons often produce a conventional neurotransmitter (glutamate, glutamate gamma-aminobutyric acid (GABA) or dopamine) and one or more neuropeptides.

The small protein-like molecules generated by neurons function in different ways; they modulate neuronal communication by acting on the cell-surface specific receptors of other neurons and this can have a number of effects on human behaviour. They can also have a biological impact on gene expression, local blood flow, synaptogenesis and glial cell morphology.

Most immune cells have surface membrane receptors for neurotransmitters, neuropeptides and hormones and they can be directly influenced by these receptors or, in the event of CNS activation, they can be indirectly

influenced by cytokine actions. Several psychiatric conditions (depression, schizophrenia, psychosomatic disorders) can cause immunological alteration whilst behavioural disturbances such as aggression and mood swings are associated with immunological changes. Furthermore, they may play a significant role in allergies and autoimmune collagen ailments, for example, systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, Sjögren's syndrome and mixed connective tissue disease. Feelings of helplessness or the suppression of negative emotions can stimulate the growth or spread of cancer.

It is worth noting that hypnosis, psychological relaxation, and classical conditioning treatments have had positive results with immune system disorders; relaxation techniques and the placebo effect have been found to stimulate Th-1 lymphocytes (1, 2).

ACTION MECHANISMS OF THE SMALL PROTEIN-LIKE MOLECULES EXPRESSED AND PRODUCED BY NEURONS

Neuropeptides, neurotrophins, neurotransmitters and catecholamines play a significant role in modulating the immune response (2, 3).

Neuropeptides

The human genome contains about 90 genes that encode precursors of neuropeptides. About 100 different peptides are known to be released by different populations of neurons in the mammalian brain (1–4).

There are 3 groups of hormones that act as neuropeptides: (i) Hypothalamic hormones (somatostatin, corticotropin-releasing hormone, gonadotropin-releasing hormone, GHRH, orexins, thyrotropin-releasing hormone, and proopiomelanocortin [ACTH, MSH, lipotropin]). (ii) Gastrointestinal hormones (cholecystokinin, gastric inhibitory polypeptide, gastrin, motilin, secretin and vasoactive intestinal peptide. Other hormones acting as neuropeptides are calcitonin, oxytocin and vasopressin and (iii) protein-like compounds with neuropeptide activity [angiotensin, neuropeptide Y, neuropeptide S, neurotensin, calcitonin gene-related peptide, and kinins (bradykinin, tachykinins)].

Neuropeptides induce the release of hormones (corticotropin, ACTH and glucocorticosteroids), monoa-

mine neurotransmitters (epinephrine, norepinephrine, dopamine), free radicals, cytokins (IL-1, IL-6, TNF), opioids, peptides, endogenous opiates and endocannabinoid antimicrobial peptides (proenkephalin, chromogranin B).

Lymphocytes have receptors for neuropeptides released by the peripheral nervous system; examples would be substance P, somatostatin, VIP and opioids. They also have catecholamine receptors. The activation of α_1 , α_2 and β_2 catecholamine receptors are able to induce humoral immunity stimulation and can increase specific IgM antibodies.

Neuropeptides also activate cell-mediated immunity, stimulating the release of T lymphocytes cytokines (e.g. IL-2), macrophage proliferation, natural killer (NK) cell activity and the endothelial adhesion of lymphocytes (4).

Along with the autonomous nervous system, opioid and antimicrobial peptides are important for regulating immune responses.

Opioid peptides. Opioid peptides are neuropeptides of short sequences of amino acids that mimic the effect of opiates in the brain (1–3). Depending on the type of peptide, the concentration, the peptide receptor and the contact time of the peptide with the immune cell, they regulate immune responses. Brain opioid peptide systems are known to have a significant influence on motivation, emotions, attachment behaviour, the response to stress and pain and the control of food intake.

Examples of opioid peptides are: dynorphin; endomorphin; endorphin; enkephalin; nociceptin; VGF, (non-acronymic genes generated *in vivo* by neurotrophins – nerve growth factor (NGF), brain derived growth factor and glial-derived growth factor).

Opioid peptides that act as neuropeptides are: cocaine and amphetamine-regulated transcript; bombesin, gastrin releasing peptide, carnosine, delta sleep-inducing peptide, FMRF amide, neurophysins, galanin, galanin-like peptide, neuromedin (B,N,S,U), pancreatic polypeptide, opiorphin, and the pituitary adenylate cyclase activating peptide.

Opioid peptides may be produced by the body or digested in food. Some endogenous opioid peptides (with more than 8 amino acids) are: β -endorphin; enkephalins; dinorphins (originally enkephalin B); and, probably, endomorphin. The human genome contains 3 homologous genes that code the endogenous opioid peptides.

The human gene for proopiomelanocortin codes for endorphins such as β -endorphin and gamma-endorphin. Enkephalins have a specific gene. Opiorphin (human saliva) is an enkephalinase inhibitor, i.e. it prevents the metabolism of enkephalins.

Exogenous opioid food peptides are: casomorphin (in milk), gluten exorphin (in gluten), gliadorphin/gliu-teomorphin (in gluten), rubiscolin (in spinach). There are also microbial opioid peptides – deltorphin I and II (fungal) and dermorphin (from an unknown microbe).

Antimicrobial peptides. Monocytes can release the antimicrobial peptides proenkephalin and chromogranin B that are able to stimulate immune cells (1, 2). They stimulate the chemotaxis and phagocytosis of the macrophages and provoke the release of pro-inflammatory cytokines (IL-1, IL-6, etc.).

These peptides can also activate T lymphocytes that induce cytotoxic cell proliferation and the secretion of immunoglobulins by the plasmacells. They are also able to activate NK cell cytotoxicity.

Proenkephalin and chromogranin B can activate neutrophils and release antimicrobial peptides, for example, defensin. They also cause central nervous pain.

Autonomous nervous system (ANS) mediators. The autonomous nervous system is composed of the sympathetic (noradrenergic) and the parasympathetic (cholinergic) systems. Chronic stress stimulates ACTH secretion that activates the secretion of corticoids, adrenalin and noradrenalin that suppress the production of IL-12 by the antigen-presenting cells, the main Th1 cell response-inducing stimulus (1–3). Corticoids have a direct impact on Th2 cells, increasing the production of IL-4, IL-10 and IL-13. This gives rise to a Th1/Th2 imbalance in favour of a Th2-cell-mediated response with the deregulation of the neuroimmunologic homeostatic mechanisms that are secondary to chronic stress. This affects cytokine expression and favours an ‘allergic’ inflammatory response. In addition to the stimulation of immediate hypersensitivity reactions, chronic stress depresses cell-mediated immunity.

Neurotrophins

Neurotrophins are a family of proteins that act as NGFs that induce the survival, development and function of neurons (5, 6). They may be considered as new cytokines. Several cells have neurotrophin receptors and may be activated by these proteins.

One of the cell receptors is Pan-neurotrophine P75 that is of low affinity. Another receptor is Tyrosine Kinase (trkA trkB trkC of high affinity) which may act as receptor of the NGF, the brain-derived neurotrophic factor (BDNF) and neurotrophins-3 and -4. Other neurotrophins have different receptors: GDNF; neurturin; artemin; persephin (GDNF receptor); and Neuregulin (1–4), GMF, CNTF, PACAP (other receptors).

Neurotrophins with high affinity to tyrosine kinase cell receptors (trkA trkB trkC) are the BDNF, neurotrophins-3 and -4 and the NGF.

The BDNF and neurotrophins-3 and -4, are neurotrophins that increase the Th2-mediated response (production of IgE) and reduce the Th1 response.

The NGF released by the sympathetic or sensory neurons may cause: proliferation of T lymphocytes and cytokines release; activation of B lymphocytes and plasma cell antibody production; degranulation and

proliferation; and differentiation of mast cells. It further activates monocytes and macrophages, quimiotaxis and the survival of cytotoxicity of eosinophils and basophil differentiation and cytokines release (Table I).

A new neurotrophin-1(NNT-1), a cytokine of the interleukin-6 family, can produce B-cell activation via gp130 receptor stimulation.

Neurotransmitters

Neurotransmitters are endogenous chemicals that relay, amplify, and modulate signals between a neuron and another cell (3, 5, 6). Several chemicals and over 50 neuroactive peptides act as neurotransmitters. Not all neurotransmitters are equally important.

Monoamines that act as neurotransmitters are: acetylcholine; dopamine; norepinephrine; epinephrine; serotonin (5-HT); histamine; melatonin; adenosine; and anandamide. Other molecules with neurotransmitter activity are GABA, glycine and aspartate.

Neuroactive peptides also have neurotransmitter activity; examples are: bradykinin, beta-endorphin, bombesin, calcitonin, cholecystokinin, enkephalin, dynorphin, insulin, gastrin, substance P, neurotensin, glucagon, secretin, somatostatin, motilin, vasopressin, oxytocin, prolactin, thyrotropin, angiotensin II, sleep peptides, galanin, neuropeptide Y, thyrotropin-releasing hormone, gonadotropin-releasing hormone, growth hormone-releasing hormone, luteinizing hormone, and vasoactive intestinal peptide.

Soluble gases (nitric oxide, carbon monoxide and zinc single ions) are not neurotransmitters but can have neurotransmitter activity.

The vast majority of psychoactive drugs exert their effects by altering the actions of the neurotransmitter system and work through transmitters other than glutamate or GABA. For example, the addictive drugs, cocaine, amphetamine and heroin primarily affect the dopamine system.

The molecules that act as neurotransmitters can be removed from the synaptic cleft of the glial cells (astrocytes remove neurotransmitters).

In humans, the sympathetic nerve system can release catecholamins (epinephrine and norepinephrine). Their effect on immune regulation is different, depending on the organ and the concentrations; there are also differences in the effect on animal models and humans. In rats, the stimulation of β_2 adrenergic receptors and norepinephrine provokes predominant TH responses. In humans, the stimulation of β_2 adrenergic receptors provokes predominant TH-2 responses.

Acute exposure to β -adrenergic agonists in low concentrations increases NK cells (number and activity) and blood lymphocytes T CD8⁺ (number but not activity). Catecholamins also decrease lymphocytes T CD4⁺ but do not affect B lymphocytes. However, chronic exposure to high concentrations in the lymphoid organs (that are more sympathetic), lowers, or does not change, the number of lymphocytes and NK cells.

PSYCHO-PHYSIOLOGICAL DISORDERS

Psycho-physiological disorders (reactive emotional states) develop when an emotional or psychological condition causes or exacerbates the physical symptoms of a disease in a direct or an indirect form (1–11). They represent the relationship between mental (psyche) and physical (physiological) processes due to the interaction between the mind and the body.

There are two main types of psycho-physiological disorders, differentiated by the physical symptoms: in the first type, sometimes known as ‘somatoform disorders’, the physical symptoms have no physical cause; in the second type, the physical symptoms have a physical cause but they are made worse by psychological issues.

Specific emotional conflicts and specific personality structures could be related to a certain psychosomatic diseases.

There are psychological and physiological reactions to internal or external disturbances. They may be directly caused by psychological or psychological pathologies or by an alteration of the autonomic nervous system. Psycho-physiological disorders can also be caused indirectly, by a psychological condition, active hormones or mixed immunological reactions (1).

Some of the more common emotional states responsible for the development of illness are anxiety, stress, and fear. Common psychosomatic ailments are: migraines; attention deficit hyperactivity disorder; ulcerative colitis; and heart disease. Hypertension is made worse by stress and there are many other conditions that are either made worse or caused by psychological problems. Minor and major stress factors are very important in the onset and course of rheumatoid arthritis, juvenile chronic arthritis, and systemic lupus erythematosus.

Table I. Cells with neurotrophins receptors

Neurotrophins	NGF	BDNF	NT-3	P57	trkA	trkB	trkC
Neural cells							
Neurons	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Schwann cell	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Glial cell	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Keratinocytes	Yes				Yes		
Immune cells							
LTh-1		Yes			Yes	Yes	Yes
LTh-2	Yes	Yes			Yes		
Activated TL	Yes	Yes			Yes		
B cells	Yes	Yes			Yes		
Basophils							
Eosinophils	Yes						
Mast cells	Yes	Yes			Yes		
Macrophages	Yes	Yes			Yes	Yes	

NGF: nerve growth factor; BDNF: brain-derived neurotrophic factor; NT: neurotrophin; trk: tyrosine kinase.

Stress can also affect clotting and induce psychogenic purpura, ecchymosis and recurrent bruising (predominates in women). Clotting problems have been reported in cases of: emotional lability, depression, sexual problems, obsession, anxiety, aggression and hostility, hypochondria, feelings of guilt, masochism, and hysteria (1, 8, 9). Stress has been shown to retard wound healing by impairing immune responses (1).

Fibromyalgia syndrome (2) represents a failed attempt of the autonomic nervous system to adjust to a hostile environment. There is a sympathetic hypo-reactivity to stress that produces an allostatic load. It has been suggested that dorsal root ganglia are important sympathetic-nociceptive short-circuit sites (10).

Psychoneuroimmunology is the study of how psychological factors influence the immune system and immune functioning (1, 12–14). There is a physiological connection between the CNS and the immune system. For example, the sympathetic nervous system innervates the immune organs of the thymus, bone marrow, spleen, and even the lymph nodes.

There are 3 types of mental disorders that may affect the immune system: (i) psycho-physiological disorders or reactive emotional states; (ii) primary psychiatric disorders; and (iii) secondary psychiatric disorders (diseases of other organs that cause psychological psychiatric illnesses).

(i) *Stress* can suppress or dysregulate immune function and increase susceptibility to disease. Several factors influence the enhancing or suppressive effects of stress on immune function (15–17):

- *Duration*: Acute stress may activate an immune response and enhance innate and adaptive immune responses. Chronic stress can suppress or dysregulate immune function.
- *Leukocyte distribution*: During acute stress, tissues that are enriched with immune cells (e.g. the skin) show immuno-enhancement; endogenous stress hormones enhance skin immunity by increasing leukocyte trafficking and cytokine gene expression at the site of antigen entry. On the other hand, depletion of leukocytes (e.g. in the blood) leads to immuno-suppression.
- *Physiological and pharmacological stress hormones*: Endogenous hormones in physiological concentrations can have immuno-enhancing effects. Synthetic hormones and endogenous stress hormones released during HPA axis activation at pharmacological concentrations are immuno-suppressive. They inhibit the production of lymphocytes, the white blood cells that circulate in the body's fluids and are important for the immune response. Chronic exposure to corticosterone or acute exposure to dexamethasone significantly suppresses skin delayed-type hypersensitivity reactions.

- *Timing*: Immuno-enhancement is observed when acute stress is experienced during the early stages of an immune response while immuno-suppression may be observed at late stages. The type of immune response (protective, regulatory/inhibitory, or pathological) that is affected determines whether the effects of stress are ultimately beneficial or harmful for the organism.

Negative emotional states produce several immunological alterations that may cause other pathologies. Alcohol, cigarette smoking, lack of physical activity and sleep disturbances exacerbate immunological changes.

Mitogen tests have shown that discussing marital difficulties can result in a decrease in NK activity, macrophages, immunity levels and can increase some T cells and blood levels of Epstein-Barr virus (EBV). Marital problems, divorce and separation have been shown to decrease lymphocyte function, T-cell effectiveness and to increase virus levels in the blood. Internal or external difficulties that alter or lead to personal problems and failure to resolve them are all causes of stress.

General adaptation syndrome (7). There is an association between a natural stressor and alterations of immunity levels that may be due to the effect of neurotransmitters and hormones secreted during stress or due to indirect causes: poor nutrition, consumption of (legal or illegal) drugs, poor personal care, etc.

Stress provokes neuronal activation of the CNS and the paraventricular nucleus; it releases the corticotrophin hormone (CHR) that inhibits T- and B-cell responses, NKT cells and causes periphery inflammation. Stress also produces adrenalin and noradrenalin that increase white blood cells and depress cell mediated immunity (Th1 responses).

Adrenergic and cholinergic neurons release vasoactive intestinal peptide (VIP), somatostatin and other hormones that decrease cell-mediated immunity and NK cells. Somatostatin also inhibits antibody production.

The activation of the hypothalamus-hypophysis-adrenal axis releases opioid peptides that decrease or increase immunological responses, depending on the receptors, the tissue and the amount. Activation of this axis induces ACTH and the release of glucocorticoids that decrease cellular and humoral immunity and have anti-inflammatory effects. ACTH also decreases antibody production and IFN and increases numbers of B and NK cells. Low amounts of ACTH regulate immunity.

Corticotrophin and glucocorticosteroids chronically affect the hypophysis-thyroid axis, resulting in lower T3 and T4 production and reduced secretion of the growth hormone that activates immune responses (7).

There are 3 categories of stressors: (i) Physical (electric shocks, swimming in cold water, physical exercise, loss of sleep, hunger, dehydration, surgical intervention, immobility etc.); (ii) Social (parental separation, isolation,

the presence of an intruder etc.); and (iii) Psychological (emotional responses, electric shocks etc.).

Stress can trigger a number of immunological reactions. Depending on the duration and intensity, stress can be described as acute or chronic. Acute stress may augment the immune system through a moderate rise in the number and activity of NK cells, an increase in lymphocytes, cytotoxic T lymphocytes, neutrophils, leucocytes, salivary IgA, IL-6 and IFN γ .

Short-term, natural stress can bring about a moderate increase in IL-6, IL-10, leucocytes and anti EBV antibodies. On the other hand, there may be a moderate decrease in NK-cell activity, mitogen induced lymphocyte proliferation (Phytohemagglutinin, concavalin A), cytotoxic T lymphocytes, neutrophils, leucocytes, salivary IgA and IFN γ .

An acutely stressful event (e.g. death of a family member) can cause a mild to moderate decrease of IL-6, IL-10, leucocytes and anti EBV antibodies; there may also be a moderate decrease in NK-cell activity. The body reacts to natural disasters, for example, earthquakes, with a moderate increase in NK cell activity, mitogen induced lymphocyte proliferation (Phytohemagglutinin) and a moderate decrease in T lymphocytes (CD4⁺ and CD8⁺).

Chronic stress increases Th2 responses but decreases T cells, Th1 reactions, NK cells, B cells and raises blood levels of EBV. Pessimistic psychological states can lower lymphocyte reactivity and T-cell effectiveness. Loneliness has been shown to reduce NK activity. Certain forms of chronic stress are associated with an increased frequency of infections of the upper respiratory tract (colds, flu, etc.). Stress related to academic demands (e.g. exams) can decrease NK cell and T-cell activity, IgA levels and increase susceptibility to the herpes virus. A psychological need for power and control can result in reduced NK activity and a lower number of lymphocytes.

Chronic physical stress (cardiac arrest, disability, etc.) causes a mild to moderate reduction in NK-cell activity, mitogen-induced lymphocyte proliferation (phytohemagglutinin, cytokines production) and there is a humoral response to viral vaccines.

In people over 55 years old, chronic stress results in a decrease in NK-cell activity and mitogen-induced lymphocyte proliferation. In people younger than 55 there is only a decrease in NK-cell activity.

Based on NK-cell activity, hypersensitive reactions and cell-mediated immunity, an evaluation of the effects of stress on the immune systems of people who are optimists and pessimists showed that optimists manage acute stress better than pessimists. However, in situations of chronic or unmanageable stress, pessimists have stronger levels of immunity than optimists. Positive life conditions: satisfying personal relationships, a solid social support network etc. can increase lymphocyte function, NK activity, immunity (mitogen tests) and the immune system response to the hepatitis B

vaccine. Good humour, happiness and laughter increase IgA, the lymphocyte count and lymphocyte activity. Hypnosis and relaxation techniques have been found to improve cell effectiveness and NK-cell activity whilst lowering stress hormone levels in blood and retarding herpes virus activity.

Physical and aerobic exercise stimulates production of white blood cells, endorphins, NK and T cells although it can decrease lymphocyte function (T-cell effectiveness). Similarly, feelings of good group and peer support can result in an increase NK-cell numbers and activity and the number of lymphocytes but can reduce T-helper cells.

People with an optimistic, practical disposition are more likely to be able to counteract the decrease of immunity (NK and T lymphocytes activity) induced by stressful events and situations.

Neurogenic stimulation of the autonomous nerve system and certain drugs (neuroleptics, antihypertensive treatments, psychotropics, anti-histamine H2 and opioids) lead to higher levels of dopamine that inhibits the production of ACTH (11).

(ii) *Primary psychiatric disorders* are rare and should be treated in conjunction with psychiatrists and psychologists. Many mental and emotional disorders involve physical manifestations that are often the first definitive sign of disease; some examples are obsessive-compulsive disorders, control impulses, depression and anxiety.

Immunological changes that have been reported in patients suffering from depression are (14–16): a moderate increase of circulating neutrophils leucocytes and activated T CD8 lymphocytes; a decrease in the number and activity of T cells and NK cells (mainly in men); an increase of IL-6 (Th-2 cytokine); a higher number of acute phase proteins (α 1-glicoprotein, α 1-antitripsin, and haptoglobin); c-reactive proteins and the expression of soluble intercellular adhesion molecules that increase endothelial activation (mainly in patients with cardiovascular disease).

A further alteration observed in depressive patients was a Th1 and Th2 cytokine imbalance. TGF-beta1 seems to influence the pathophysiology of depression. Melancholic depressed patients release less IL-1 β than those that are not melancholic.

Depression also affects the autonomous nervous system and hormonal release. There is an activation of the peripheral sympathetic nervous system and elevated levels of catecholamines and neuropeptide-Y. Immunity against viral infections inside the cells is reduced. Cell mediated immunity decreases but humeral responses to bacterial infections outside the cells increases.

Hormonal changes are characterised by inhibition of the effects of the corticotrophin-releasing hormone (CRH) and the corticoids do not function, due to a defect of the glucocorticoids receptors.

Depression is associated with lower levels of serotonin: a decrease of tryptophan, the precursor of 5-hydroxi-

triptamine (serotonin) correlates with the severity of the depression. Cytokine (IFN- γ) activation induces indoleamine 2 and 3-dioxygenase, a tryptophan degradation enzyme that leads to tryptophan catabolism and reduces the availability of tryptophan for serotonin synthesis.

Antidepressant treatment associated with clinical improvement alters the Th1/Th2 balance through the action of TGF β 1. Tricyclic antidepressants that are associated with clinical improvements increase NK cells and decrease IL-6 (Th-2 cytokine), causing a shift in Th-1 responses. There are several studies on the treatment of depression; they include the use of IL-1 receptor antagonists, anakinra (an IL-1 receptor antagonist), anti-TNF antibodies (infliximab) and receptors (etanercept) and anti-inflammatory cytokines (IL-10). Other options are the antidepressant targeting of the corticotrophin releasing factor, therapies targeting monoamine neurotransmission with anti depressants inhibitors of indoleamine 2,3-dioxygenase, the inhibition of inflammatory signals with enhancement of glucocorticoid signalling and the use of type 4 phosphodiesterase inhibitors (14, 15).

Schizophrenia is frequently associated with autoimmune diseases such as rheumatoid arthritis – patients produce less IL-2 and IFN- γ , there is a switch Th1 to Th2 that alters the availability of tryptophan and serotonin and there is a disturbance of the kynurenine metabolism with an imbalance in favour of the production of the N-methyl d-aspartate receptor antagonist, kynurenic acid (16).

(iii) *Secondary psychiatric disorders* (disease of organs, causing psychological, psychiatric illnesses) (15–19) are rare and should be treated in conjunction with psychiatrists and psychologists. These diseases affect appearance and/or alter the quality of life of the patient; they may cause feelings of shame, depression, anxiety, low self-esteem, and suicidal ideation. Patients may have to deal with discrimination and social isolation. They sometimes have difficulty obtaining work.

Many psychological and emotional disorders have physical manifestations that are often the first definitive sign of disease: obsessive compulsive disorders, impulse control, depression, anxiety, body dysmorphic disorder, anorexia nervosa, and tobacco dependence (19).

Dysmorphophobia is an abnormal preoccupation with a real or imagined body image defect. The most common eating disorders are anorexia nervosa, bulimia, and compulsive eating. Burning mouth syndrome (glossalgia/glossodynia) is associated with depression and anxiety (62% of cases) and cancer phobia (20–30% of cases). It is also symptomatic in personality disorders, mood swings, anxiety, etc.

Stress can affect clotting and lead to psychogenic purpura, ecchymosis or recurrent bruising (predominates in women). Clotting problems have been associated with: emotional lability; depression; sexual problems; obses-

sion; anxiety, aggression and hostility, hypochondria, feelings of guilt, masochism, and hysteria.

INTERACTION OF THE NERVOUS SYSTEM AND THE SKIN

Recent studies have highlighted the role of emotion dysregulation in several skin diseases. There is a considerable amount of published scientific literature concerning psychological distress and dermatological diseases. Psychocutaneous diseases are common.

The skin and the CNS have a similar embryological origin. They both release common neuromodulators, peptides and biochemical systems. For this reason, the skin is an organ that is strongly reactive to psychiatric and psychological conditions and this interaction may be significant in the pathogenesis of several skin diseases (16, 17).

Psycho-physiological disorders (18)

Psychological illness may alter the evolution of a skin disease, precipitating its appearance or exacerbating an injury. Some examples of psycho-physiological skin manifestations are flushing, facial pallor and hyperhidrosis; a number of dermatoses can be aggravated by stress and psychological disorders: skin infections (herpes virus, warts, fungi), tumours, allergies, atopy, urticaria, angioedema, psoriasis, vitiligo, alopecia, acne, seborrhoea, seborrhoeic dermatitis, and rosacea.

Atopic dermatitis is associated with stress (70% of cases), anxiety, depression and neurosis. Psoriasis is associated with stress (39% of cases), anxiety, depression, obsession, and alcoholism. Hives and angioedema are associated with stress (51–77% of cases), hostility, rage and depression. Alopecia areata is associated with stress (23% of cases), anxiety, depression and paranoia. Chronic stress also weakens the immune system and this may affect the incidence of virus-associated cancers, for example, Kaposi's sarcoma and some lymphomas.

Cutaneous primary psychiatric disorders (19, 20)

These refer to skin conditions that have been self-inflicted by patients with psychiatric disorders. Examples are self-inflicted dermatoses (trichotillomania and onicofagia), factitious injury or neurotic abrasion/excoriation (skin-picking), dermatillomania, acne excoriée, neurotic excoriatio, and psychogenic excoriation.

Secondary psychiatric disorders (21)

Skin conditions that affect the psyche may cause depression, frustration and social phobias. They may occur in patients with psychological problems and have a negative impact on their self-esteem and body image. They include the disfiguring skin disorders:

severe acne, big lips, rosacea, rhinophyma, angiomas and giant hairy pigmentary naevus.

THE NERVOUS SYSTEM AND SKIN DISEASE

Pruritus (22, 23)

Itching is an unpleasant sensation, similar to pain, that can be local or generalised. It is a complex sensory and emotional experience produced by primary psychiatric disorders or psycho-physiological disorders such as itching of the scalp and trichotillomania, prurigo, and anal itching.

Pruritus may be caused by: medication, allergies, pregnancy, dry skin, poor nutrition, cancer, infection, psoriasis, diabetes, aging, collagen diseases, and gastrointestinal disorders. It can also occur in association with other conditions like Crohn's and Behçet's disease

There is a need to define psychogenic pruritus and its diagnostic criteria. Nerve diseases can cause neurological itching as with neuropathies, or disorders of psychic mania, anxiety, sexual problems, psychiatric conditions, etc. (23).

Functional brain imaging studies have identified brain regions associated with pruritus and found that several regions are activated by itch stimuli. The possible roles of these regions in itch perception and differences in the cerebral mechanisms of healthy subjects and chronic itch patients have been discussed. The central itch modulation system and cerebral mechanisms of contagious itch and the pleasurable sensation evoked by scratching have also been investigated.

Several nervous system mechanisms might be responsible for itching. Cholinergic fibres release acetylcholine and produce VIP which causes the eosinophil to release histamine and activate the peripheral itching receptors located in the epidermis. The histamine stimulates the H₂ and H₃ brain receptors and activates the neurons of the CNS which secrete opioid peptides that also stimulate the peripheral itching receptors. Moreover, type C sensory nerve fibres, are also activated, they release the neuropeptides, Neurokinin A, substance P and the NGF that activates the pruritus receptors. Itch receptors can also be indirectly stimulated by the IL-2 and prostaglandins.

Vitiligo (24–26)

In cases of vitiligo, melanocyte damage is produced by immunological and neurogenic factors and self-destruction. The disease is mediated by T cells and accelerates with stress, personal trauma, exposure to UVR and mechanical injury.

The shock protein, caloric HSP70, is released by the CNS and damages melanocytes, releasing antigenic proteins that activate dendritic cells, inducing a T₄ and T₈-cell immune response and further releasing

pro-inflammatory cytokines and nitric oxide that cause destruction of melanocytes, accelerating the depigmentation. Melanocyte damage can also be caused by the release, by the brain, of the peptide associated with calcitonin (CGRP), which stimulates the neuropeptide and harms the melanocyte. The activated adrenergic fibres release norepinephrine, epinephrine, dopamine, metanephrine, and H-indol acetic acid that increase in cases of vitiligo and damaged melanocytes. This is added to by the fact that type C nerve fibres release neuropeptides (NGF) that also harm the melanocytes.

Alopecia areata (26, 27)

Stress is an important factor, especially when the disease itself produces psychological stress. Psychiatric disorders are observed in 67% of cases (1).

The high level of psychiatric morbidity plays a pathogenic role. Problems of adaptability have been detected in 43.2% of cases; dependent personality (66% of cases); antisocial personality (39%); anxiety (41.1%); and depression (32%). In contrast, generalised anxiety and a depressive personality are noted in less than 1% of patients.

Alopecia areata is an autoimmune disease mediated by T and B cells. There are immune responses to the antigens of the hair follicles. The auto-antigens of the hair follicle are the peptides associated with melanogenesis (trichohyaline and specific keratin). The condition is associated with HLA or immunogenic and neuroendocrine factors.

The hair follicle has a natural protection against immuno-allergic reactions that can cause damage (immune privilege). The hair follicle contains immunosuppressive factors (TGF- β 1 and β 2, ACTH and MSH α). There is a small presence of NK cells, lymphocytes CD4⁺ and CD8⁺, and an absence of Langerhans cells and lymph vessels. Immune privilege prevents allergic reactions to hair follicle melanocytes and keratinocytes that do not express MHC I by inhibition of activating molecules.

Immune privilege may fail due to micro-trauma, follicular damage, bacterial superantigens, viral infections and psychological alterations. The loss of immune privilege stimulates allergic reactions and the recognition of autoantigens, T lymphocytes and NK cells which release inflammatory cytokines. Stress inhibits the production of ACTH, α -MSH and the ACTH-releasing hormone, resulting in follicle damage and alopecia areata

Another psycho-immunological mechanism that can cause alopecia areata is the release of the peptide associated with the calcitonin gene (CGRP) by type C and sympathetic fibres. This peptide stimulates the immune response Th-1 (lymphocytes CD4 helper) and inhibits Th2 lymphocytes. Stimulation of B lymphocytes that produce IgG antibodies originates an immune complex which induces apoptosis in keratinocytes of the hair follicles, causing alopecia.

Psoriasis (28, 29)

Both internal factors (heredity, hormone metabolism, the nervous and immune systems) and external factors (trauma, infections, cutaneous flora, antigens, ultraviolet radiation, drugs, alcohol, tobacco, etc.) can trigger the condition, which is caused by an increase in the proliferation of epidermal keratinocytes. Psychological itching and sleep disturbances may occur in 80% of psoriatic patients. Depression is common in severe cases. There is also a direct relationship between stress, the severity of cutaneous manifestations and joint commitment in psoriatic arthritis. The prevalence of depression in patients with psoriasis is estimated to be between 10 and 62%.

Several psycho-neural mechanisms may cause psoriasis; sensory nerves release neuropeptides (neurotensin, somatostatin, substance P and NGF) which activate the proliferation of keratinocytes. Sensory nerves and C-fibres also release CGRP (α -calcitonin gene-related peptide), which directly activates keratinocyte proliferation and stimulates the endothelial cells. The C-fibres further release nitric oxide and cholinergic fibres produce acetylcholine and the vasoactive intestinal peptide (VIP); all of them are linked to vasodilatation.

Neuropeptides activate granulocyte and macrophage (GM-CSF) which attract the macrophages and monocytes that secrete prostaglandin PGE₂ and interleukin IL-10. In addition to producing increased proliferation of keratinocytes, these neurotransmitters stimulate T cells and vasodilation.

The Koebner phenomenon occurs when scratching causes the release of neurotransmitters.

Hyperhidrosis (excessive sweating) (30, 31)

Sweating is a multifunctional response that aids locomotion, thermal regulation, self-protection and the communication of the psychological state. The primary stimulus is heat. Secondary stimuli may include emotions and certain foods (seasoning and spices).

Normal sweating is caused by the activation of the CNS and an effector or peripheral system. The amygdala, cingulate cortex, and medulla participate via efferent fibres that descend the spinal cord and connect to preganglionic sympathetic neurons in the nucleus intermediolateralis. In the brain, there is a temperature controller, located in the pre-optic area of the anterior hypothalamus, which has thermoreceptors with neurons sensitive to temperature changes. When these receptors are activated, a signal passes through the spinal cord and connects to preganglionic 12 and 13 sympathetic neurons, which release acetylcholine that stimulates the sweat glands through gland eccrine-capillary interaction.

Excessive sweating can be located in the feet, the sacral region, axillae, trunk, face and scalp. When it

affects an area > 100 cm² it is considered as widespread. Hyperhidrosis can be primary or secondary. Primary hyperhidrosis (or hyperhidrosis of unknown origin) is more frequent, and usually has a social impact. The condition may start in childhood or adolescence it can become more severe in puberty and persist throughout life. Secondary hyperhidrosis (or diaphoresis) is associated with febrile infections, drugs, endocrine problems and psychological disorders. Psychiatric or psychosomatic conditions that can accompany hyperhidrosis include: migraine, emotional problems, nervous agitation, night sweats, hysteria, panic, and depression.

To date, the central pathways of emotional sweating have not been elucidated. The limbic system, including the amygdala and cingulate cortex, is critical for emotional processing and many cognitive functions. Measurement of sweat output on the palm or sole is useful for evaluating sympathetic function and limbic activity in autonomic and psychiatric disorders.

Acne (3, 32, 33)

Acne involves skin, hormonal, immunological and psychological factors. Stress can induce and exacerbate acne lesions. Cutaneous lesions can have a psychosocial impact and alter the nervous system. Both the peripheral and CNS are associated with cutaneous factors and the action of androgens in the formation of comedones.

Acne and seborrhoeic dermatitis may be caused by a neurogenic stimulation of sebaceous secretion. Sensory nerves release neuropeptides (neurotensin, somatostatin, substance P, NGF, hormone melanocyte, and PPAR- γ) stimulant- α and the peptide derived from the proopiomelanocortin, all of which stimulate sebaceous gland sebocytes, increasing secretion. The activated sebocytes also secrete cytokines (IL-1 α , IL-6, TNF- α , INF- γ and PPAR- γ) that produce inflammation.

Seborrhoea or excessive sebaceous secretion and seborrhoeic dermatitis may increase sebum production through a neurogenic mechanism similar to acne.

Rosacea and red face syndrome (flushing) (34, 35)

The nervous system can instigate vasomotor reactions. Shock may result in vasoconstriction, causing facial pallor. Psychological reactions can cause vasodilation which is clinically manifested as blushing, facial redness, erythrosis or persistent or chronic blushing that can lead to rosacea.

Vasodilatation can be produced by neuropeptides (released by the sensory nerves), nitric oxide (released by nerve C-fibres) and acetylcholine and vasoactive intestinal peptide (released by the cholinergic fibres).

Vasodilation induced skin diseases of psychological origin include vasomotor rosacea, vasomotor instability, and facial erythroaesthesia. A rosacea inductor

would be a single gene that controls enzyme mediators, neurotransmitters and cytokines.

In cases of rosacea, the nervous system, physical and chemical agents, keratinocytes and some microorganisms produce inflammation that cause vasodilation and increased vascularity. Vasodilation can produce repeated and persistent erythema which can change tonality and intensity.

Persistent vasodilatation generates angiogenesis and originates telangiectasia and dermo-hypodermic alterations. Psychological factors that aggravate rosacea are emotions, stress, an accelerated lifestyle and neurovegetative disorders.

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