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1 Psychoneuroimmunology PNI

As Andrawis (2018) mentioned, PNI psychoneur immunology is an interdisciplinary new field of research that has emerged over the last 20 years and deals with the interactions of the entire body systems that are inextricably linked. There are various disciplines in this field, such as neurochemistry, neurophysiology, neuroanatomy, molecular biology, endocrinology, psychology, psychoanalysis and clinical psychosomatics. These disciplines have a common mood.

This science is based on the fact that the body cells constantly communicate with each other and that the brain is also connected to the immune system.

The physical, mental and spiritual levels belong together. They are one unit and this was also experienced by early humans. This realization lives in the traditions of many cultures, it is also the basis of all great healing systems of the East. In orthodox medicine one cannot examine the human soul and its spirit with a scalpel and microscope.

Man is embedded in a network of different systems - the immune system, the hormone system, the nervous system and the psychosocial systems. Man is not created as a loner but is dependent on a social environment and thus lives in social structures (Andrawis A, 2018).

Ader, a pioneer (1975, 1982, Ader et. al. 1990) of the field of psychoneuroimmunology (PNI), coined this term in a series of experiments on rats and tested the conditionability of the immune system. These experiments were often repeated and confirmed by clinical studies. For example, the immune-inhibiting effect of glucocorticoids has been known for a long time and has been used by psychotropic drugs, but also other different substances, such as thyroid and sex hormones and serotonin, which all have an influence on the immune system. The immune system is not always stable, but dynamic and highly sensitive in its function as defence. This is exactly why a research development in the PNI was developed. It is examined which cellular substances of the immune system are present, which play a special role in the investigation of social and psychological stress.

In earlier psychoimmunological studies, T (or B) lymphocytes were stimulated and their function was determined in vitro. Recently, deep layers of T lymphocytes and their interrelationships, the T4 helper cells, have been quantitatively identified. These cause the increase of immune defence and the production of antibodies. T8 suppressor cells have the ability to reduce immune response and autoimmunity disease. The task of T lymphocytes is to kill the cytotoxic infected cells. It is also interesting to continue research on "natural killer cells". Why are the changes in the immune system caused by stress to be discussed?

This can be seen in the case of an imminent loss of a close relative, induced or experienced stress. It can lead to depression and social isolation. Various stressful life events lead to a weakening of the immune system.

Several experiments with rats have also shown that psychological factors such as helplessness and hopelessness weaken the immune system enormously. Conversely, successful coping with stress has a very positive effect on health.

One can therefore conclude that psychotherapeutic or other "stress-reducing" aids strengthen the immune system and thus exert a positive influence on threatening or existing illnesses.

According to various follow-up examinations, psychotherapeutically treated patients become ill less frequently and go to the doctor less frequently (ibid.).

Can the question be asked whether the immune system is autonomous?

Our immune system, which has become the focus of interest due to a variety of diseases, is the place where researchers discovered that it is part of a complex network. In the past, it was believed that the immune system was autonomous. Today we know that it interacts electrically with the psyche via nerve impulses as well as biochemically via neurotransmitters (messengers). This paradigm shift took place in the USA and coined the name psychoneuroimmunology.

The immune system is woven into the whole organism. The various immune cells that do their work for the body's defence are created in the organs (ibid.).

Systems involved

Psychoneuroimmunology (PNI) consists of the four supersystems:

- Immune System
- hormonal system
- nervous system
- Psychosocial Systems

1.1 Immune system

The immune system is referred to as the body's own defence mechanism. This prevents tissue damage, pathogens and inflammation.

The antibody that has penetrated human organisms from the microorganisms is therefore alarmed and destroyed by special cells. Since the defence mechanisms play an important role for healthy people, the immune system has always been a research topic.

The organism is protected by three different systems that complement each other:

1). The specific immune system

2.) The non-specific immune system

3). The unspecific cellular systems (ibid.).

1.1.1 The specific immune system

The specific immune system reacts to cellular, particulate and molecular foreign substances (antigens) and attacks the foreign bodies. The result is a so-called antigen-antibody reaction.

Over the course of time and due to various diseases/inflammations, these defence mechanisms against viruses or new diseases have adapted and specialised in them. The acquired specific defence mechanisms also belong to the acquired immune system. Due to their adaptability, the cells are able to form specific defence mechanisms (antigens) in order to recognise foreign bodies and build up new antibodies which attack the antigen. There are still two groups of cells that play an important role in defence, namely T-lymphocytes and B-lymphocytes.

These two types are responsible for each defence measure.

After infection, specific antibodies and memory cells are retained so that they can react within a short period of time to renewed interventions by foreign bodies.

The adaptive immune system cannot replace the innate immune system, the two complement each other. The complex immune reaction consists of the combination of adaptive and innate defence (ibid.).

1.1.2 The non-specific humoral immune system

This system consists of a complement system as well as other plasma proteins. They have the ability to dissolve the antigen-antibody complex, kill foreign cells and activate their own cells. They play an important role in the healing of inflammations and tumours. If an immune reaction occurs, this is done with the help of 9 plasma factors, the so-called complement C1 - C9.

Lysozymes have an important function, namely the inhibition of bacteria and viruses, which multiply in various tissues and body fluids such as reactions in the oral mucosa. This mucolytic lysozyme has a basic enzyme with a high concentration in the granules of polymorphonuclear leukocytes and in the macrophages of lung tissue.

During bacterial infections, increased reactive CRP (C-reactive protein) occurs (21000 MG).

Interfron is the specific group called glycoproteins. An infection, especially with viruses, leads to an increase of glycoproteins from 20000 MG - 30000 MG.

Natural antibodies are found in the plasma. These antibodies react to foreign substances on the assumption that the organism has never had contact with them (e.g. blood group agglutinins). Therefore one speaks of natural antibodies (ibid.).

1.1.3 The unspecific cellular systems

They represent the potential abilities of the white blood cells for phagocytosis. They are particularly pronounced in neutrophil granolocytes and monocytes.

Macrophages and phagocytic leukocytes destroy the pathogens and activate the antigen-antibody complex mechanisms. Tissue macrophages belong to this system. The macrophages recognize foreign substances through their specific immune system. In contrast to the specific defence systems, the non-specific defence systems destroy the foreign bodies without direct contact. The specific ones, on the other hand, react when there is a conflict with the foreign body (acquired immunity) (ibid.).

1.1.4 Specific defence mechanisms

This system includes the lymphatic system, which is divided into three main groups: B lymphocytes, zero cells and T lymphocytes. The lymphocytes develop from stem cells that are lymphatic. These are found in the liver during adolescence and later in the bone marrow.

B lymphocytes are unknown in humans, but they are located at the

Outgoing bowels of birds. T- and B-lymphocytes migrate together through the blood into the spleen and also into the lymph nodes.

B-cell system: 15 % of the B-lymphocytes are in the blood. The humoral immune reaction is caused by them. T-cell system: 70 - 80 % of the T-lymphocytes are in the blood. These have an influence on the cellular immune reaction and are not always found in the blood, but in secondary lymphatic organs.

In the case of antigen stimulation, they multiply and divide into T-effectors or T-memory cells. The T-memory cells circulate in the blood and recognize the antigens after one year.

The 10 % lymphocyte-like cells are called zero cells. They differ from the B- and T-lymphocytes by their surface. Killer cells also belong to the zero cells. They have receptors for the Fc component of IgG and destroy IgG-loaded cells. K cells then attack the body's defence system.

Immune reaction of the immediate type: All allergic forms of bronchial asthma and transfusion of unequal blood group, reactions to pollen (hay fever) and drugs. In contrast to this rapid reaction, the immune response takes place within 48 hours. This is also known as a delayed immune response.

Antigens are those harmful substances or foreign proteins that penetrate the organism. Thus specific antibodies are formed and triggered at the same time. An antibody-antigen reaction is also known as an antibody-antigen complex. An antigen loses its damaging effect through the connection with the antibody. This is referred to as neutralisation (ibid.).

1.1.5 Immunity and Allergy

If the organism is strong enough and, through its defence mechanisms, able to fend off foreign substances without a pathological reaction, then we speak of immunity. Repeated exposure to a foreign substance often leads to an allergic reaction of the organism. This can result in an increased, weakened or missing reaction. An allergy is a hypersensitive reaction. It triggers an antigen-antibody reaction. This leads to an increased cappilar premeability and thus to an increase in blood flow to the mucous membranes and skin. In the case of blood that is incompatible with groups, damage to the cappilar walls due to the deposition of immune complexes or foreign proteins in vaccine sera, secretion of exocrine glands and bronchiospasms is increased. Rejection reactions against transplants can also occur (ibid.).

1.2 The Nervous System

The nervous system is a switching and communication system that is present in humans and animals. Without the nervous system there is no exchange of information and no coordination of information in the organism.

Our behaviour is influenced by the nervous system.

The nervous system can be divided into the central nervous system, consisting of spinal cord and brain and the peripheral nervous system. The nervous system transmits information from the brain to the periphery or to the internal organs through nerve pathways, the so-called pyramid pathways. In turn, the extra pyramidal pathways transmit information from the periphery or from the internal organs to the brain (Andrawis A, 2018).

Nervous System

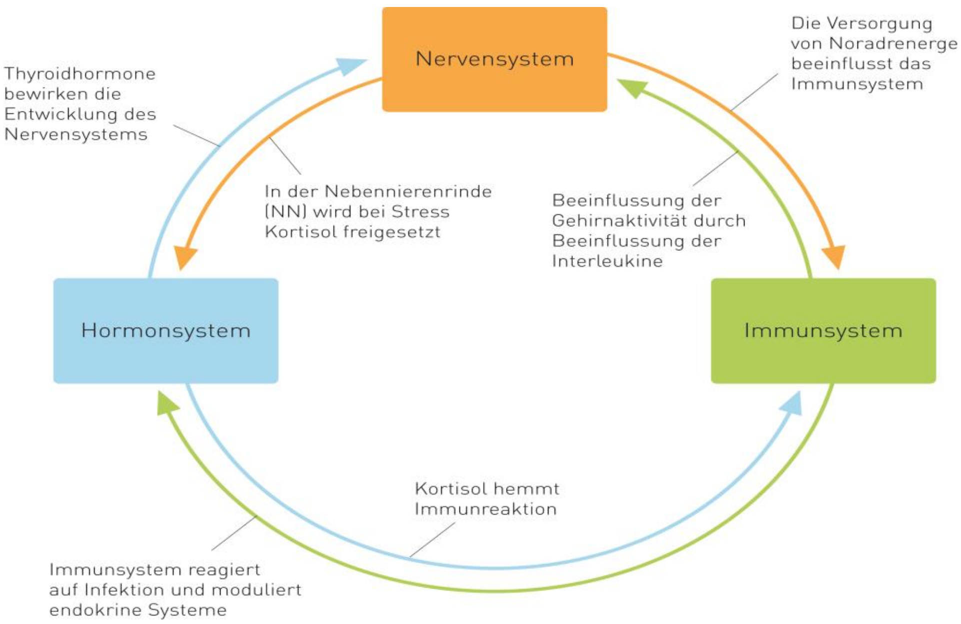

Fig.7 Cortisol - immune response - nervous system and hormone system

Source: not modified taken from (Fritzsche & Wirsching 2006: p. 13)

1.2.1 Peripheral and Central Nervous System

Both are anatomically separated. The PNS includes the nerve cells, nerve fibres and nerve tracts originating from the brain and spinal cord. The brain and spinal cord belong to the CNS. Physiologically, the sensomotoric nervous system differs from the vegetative nervous system.

The sensorimotor nervous system is responsible for receiving sensory impressions such as hearing, tasting, touching, seeing and feeling. These sensory organs stimulate receptors or organs. These are perceived via the nerve tract systems and transmitted to the CNS (ibid.).

1.2.2 Vegetative Nervous System VNS

Also known as autonomic nervous system. All body organs, except the skeletal muscles, are innervated by the autonomic nervous system.

It regulates the control processes within the organism.

The autonomic nervous system controls blood pressure, the heartbeat, the release of numerous hormones, the function of the gastrointestinal tract and the glands.

The autonomic nervous system contains two subordinate mechanisms:

The sympathetic and parasympathetic nervous systems. They are antagonists in their function. Everything that leads to stress is influenced by the sympathetic nervous system, in contrast to the parasympathetic nervous system, which provides harmony in the organism. The medulla oblongata controls the activity of the sympathetic and parasympathetic nervous system. The arbitrary activities of the nerve cells that regulate the autonomic nervous system are found in the brain stem (Andrawis A, 2018).

1.3 Psychosocial System

The psychosocial system is everything that places a psychological burden on a person. Stress triggering emotions, such as fear, anger, anger cause illness. The consequences of stress lead to depression and helplessness. This complex of actions also influences the other systems mentioned above. The psychosocial systems have a negative interaction with the immune, hormone and nervous systems. Long-term psychological stress leads to many illnesses.

Psychosocial stress

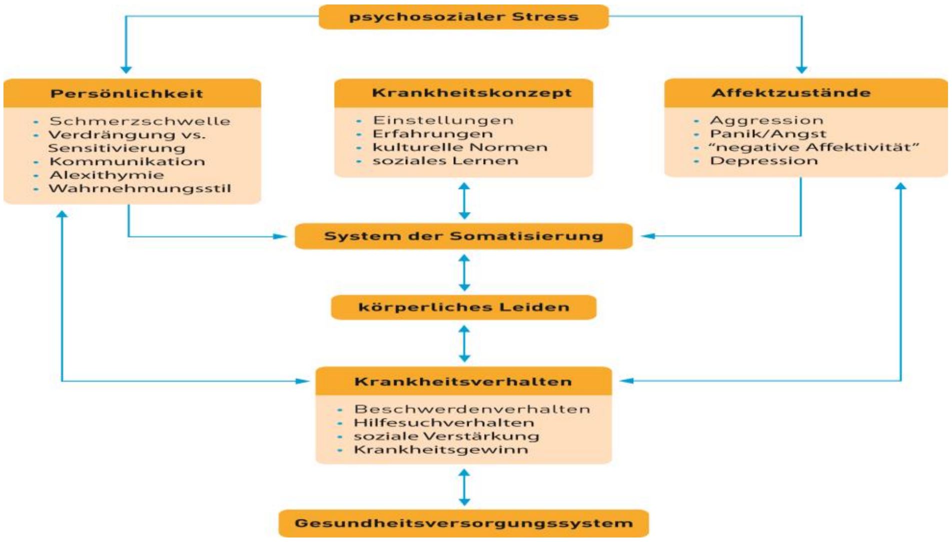

Fig. 6 Influence of psychosocial components on the organism

Source: not modified taken from (Möller et al. 2005: p. 255)

1.3.1 Psychosomatics and Social Classes

In the USA, New York (Midtown-Manhattan-Study, Michael 1960) and Canada (Stirling-County-Study, Leighton 1963) psychiatric and psychosomatic samples of the total population took place in the sixties, as well as a study of a representative population group.

For the individual disorders, the class affiliation was also noted. The research found that severe psychosomatic symptoms were more common in the lower classes than in the middle and upper classes. In Canada, however, these results were significant only among women. A correlation between the frequency of psychosomatic complaints and symptoms of social crises was found within the community.

However, the question can be asked as to whether psychosomatic disorders also exist among members of the lower classes.

The common symptoms observed in Canada were in the gastrointestinal tract, cardiovascular system, headache and musculoskeletal system. These epidemiological studies were already carried out in the 1950s by American psychiatrists and sociologists (Freedman and Hollingshead) and confirm the fact that mental and physical complaints were the most common symptoms in the lower classes and strata (ibid.).

1.4 Hormone System/Endocrine Organs Hormones as Information Carriers

Two different information systems are available for the entire coordination and function of all body cells: The endocrine system and the nervous system. The nervous system is similar to a complicated technical communication system, where information is transmitted and processed via a conduction path. The information is transmitted through nerve pathways and converted into chemical signals. This triggers a reaction in certain organs. In contrast, the endocrine system can be compared to a remote control communication system. The transmission of the messages takes place via encrypted chemical structures and continues via the bloodstream into the body cells. There it causes a certain reaction. The chemical information carriers produced by endocrine organs (inner secretory glands) are called hormones. These hormones are either proteins, steroids, tyrosine derivatives or peptides.

1.4.1 Endocrine organs Hypothalamic-pituitary system

The hypothalamus in the diencephalon is located in the middle between the cerebellum and the cerebrum.

The regulation around the preservation and reproduction respectively the working readiness of the organisms are controlled by the vegetative nervous system as well as by the endocrine system. This cooperation of both systems is mediated by the hypothalamus. The superior vegetative centres influence the sympathetic and parasympathetic nervous systems and at the same time the hormone release of the pituitary gland.

Pituitary gland and hypothalamus together form a superior functional unit over the entire hormone regulation (ibid.).

1.4.2 The pituitary gland

The pituitary gland is located in the middle skull fossa and belongs to the endocrine system. It is divided into two lobes:

Pituitary posterior lobe (neurohypophysis) and pituitary anterior lobe (adenohypophysis).

Not only its own hormones are produced, but the pituitary gland also influences the hormone production of other endocrine glands. Both lobes are directly connected to the hypothalamus via the pituitary stem. Hormones are stored in the pituitary gland, where they are formed and transported by the nerve connection in the blood. Furthermore, various hormones are produced in the anterior lobe. These hormones act on the body tissue and other glands. The transport control starts from the hypothalamus, through a special vessel the hormones reach the front lobe. The anterior lobe then takes over its work independently and monitors the hormone balance. If the hormone level of the thyroid gland is sufficiently high, for example, the pituitary gland temporarily stops the production of hormones by the thyroid gland (ibid.).

1.4.3 The thyroid gland

The thyroid lies below the larynx in the cervical area and produces two hormones: thyroxine and triiodothyronine. They reach the body cells through the bloodstream. These two hormones are important for cell energy turnover and protein production. In order to fulfil this task, the thyroid gland needs iodide ions, which are supplied by the blood. These are converted into iodine by an enzyme called peroxidase. The thyroid gland stores iodine. This process can be slower or faster than normal. If the speed of energy conversion is too fast, this is referred to as hyperthyroidism. It comes to an undesirable weight gain. If this process is slower than normal, we speak of hypothyroidism (hypothyroidism). An undesirable weight loss occurs. The increased values bring a psychological strain with various psychological symptoms, as well as vegetative and somatoform disorders (ibid.).

1.4.4 The parathyroid gland

The parathyroid gland is located at the range of the thyroid gland and produces the hormone parahormone. Its function is to regulate the calcium balance. Calcium is an important building block for bone and tooth formation, as well as for nerve and muscle cells and blood clotting.

Vitamin D, which is produced in the skin by the influence of light, helps the parathyroid gland to absorb calcium from food. In the event of an undersupply, calcium is stored in the bones and used to fulfil the function of the thyroid gland.

1.4.5 The adrenal gland

The two adrenal glands lie at the height of TH 11-12, like caps on the kidneys. They regulate the salt and water balance of the body. The adrenal glands consist of two parts: The adrenal medulla produces the hormones noradrenaline and adrenaline. The adrenal cortex produces glucocorticoids, mineralocorticoids and androgens. In case of stress, adrenaline is released into the bloodstream. This activates the VNS.

The glucocorticoids influence the carbohydrate, fat and protein metabolism. They provide the brain and heart with energy and glucose in an emergency situation (ibid.).

1.4.6 The sex hormones

Sex hormones can be divided into male sex hormones and female sex hormones and are primarily responsible for maintaining the species.

Androgens are male sex hormones that occur in both men and women. Androgen production is increased by an increased concentration of ACTH in the blood in the adrenal cortex.

The male sex hormones are called androgens and are classified as C19 steroids. These are formed in the Leydig intermediate cells in the testicles. The most important male sex hormone is testosterone.

The female sex hormones are produced in the ovaries. In the epithelial cells of the follicles oestrogens are formed under the influence of gonadotropins, and in the corpus luteum progestins. Estrogens are C18 steroid hormones. After their formation in follicular epithelia, they are released into the bloodstream under the influence of LH androgens, which are converted into estrogens under the effect of FSH. In addition, estriol is produced in the liver and estrone in the ovary. In blood plasma, more than 95% of oestrogens are bound to proteins.

Another important sex hormone is progesterone. Progesterone plays a major role in the cyclic changes of the uterus (ibid.).

1.4.7 The Pancreas

The location of the pancreas is the upper abdomen, below the stomach. It connects the small intestine with the liver through various channels. This gland consists of an endo-exocrine part. The endocrine part, called Langerhans Island, is responsible for the synthesis of four hormones, which are released into the blood. The B cells produce insulin (approx. 60%), the A cells produce glucagon (approx. 25%), the D cells produce somatostatin (15%) and an additional cell type produces polypeptide.

The exocrine part produces digestive juices, an enzyme-containing gene that is introduced into the duodenum. This is an essential contribution to the digestive tract.

1.4.8 Insulin

Insulin was discovered in 1921 by BANTING and BEST. It is a polypeptide molecule (approx. 5800 Da) and consists of two different peptide chains. A is composed of 21 and B of 30 amino acid residues.

The insulins are released in the blood by a certain stimulus. This leads to an increase in the blood glucose level. At the same time, a plasma concentration causes an increase in amino acids and gastrointestinal hormones (e.g. GIP, gastrin, CCK) and thus leads to insulin secretion. The vegetative nervous system influences this release through its two mechanisms: sympathetic impulses inhibit insulin secretion, parasympathetic impulses excite and increase alpha and beta receptors.

Insulin is an anabolic hormone which is vital and promotes growth. It is responsible for the absorption of glucose and amino acids in cells and inhibits the degradation of glycogen and fat. The glucose concentration in the blood is lowered by all metabolic effects of insulin (ibid.).

1.4.9 PNI and the effect of stress on the hormonal system

The immune system influences, among other things, the nervous system and vice versa. Both systems also influence all other hormonal systems - an increase in the concentration of cortisol and adrenaline in the blood leads to dysfunction of the organisms, especially in the hormonal system, which in turn has a negative effect on the kidneys and adrenal glands.

The psychosocial processes can also trigger stress-accompanying and stress-triggering emotions (chronic suffering, anxiety, anger, rage). Here stress appears as depression and helplessness. Chronic stress has a negative effect on all systems mentioned above and promotes the development of various diseases. Also the healing slows down or is prevented.

1.4.10 Effect of stress on the vegetative nervous system VNS

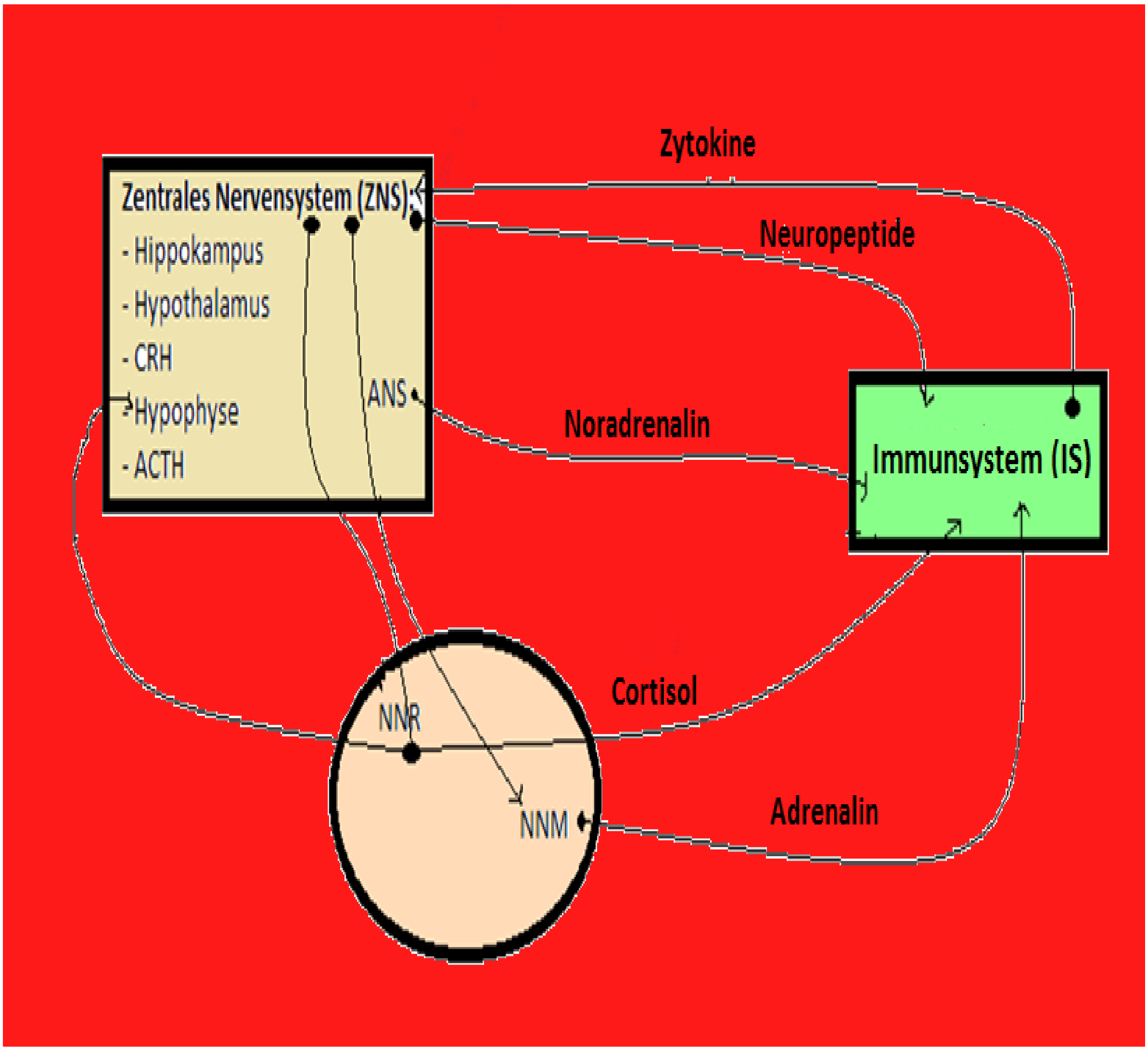

Fig. 1: Participating systems and hormones: The immune system is not an autonomous system.

Source: Own modified image representation of stress and VNS relationships (Andrawis A, 2013).

During stress, impulses are sent via the CNS to the adrenal medulla NNM and the adrenal cortex, which release cortisol and adrenalin.

The immune system reacts by increasing the concentration of cortisol and adrenaline in the blood. This increase in concentration can lead to an increased alerting of the body's immune system. Feedback between the immune system and the CNS takes place via cytokines and neuropeptides.

Another important system to react to stress is the hypothalamus-pituitary-adrenal axis. The hypothalamus-pituitary-NN-axis is a negative feedback loop that includes the hypothalamus, the pituitary gland and the adrenal gland.

Corticotropin-releasing factor (CRF) arginine vasopressin (AVP) and adrenocortonotropin hormone (ACTH) are the central messengers. Cortisol exerts a negative feedback on the hypothalamus and pituitary gland. Cortisol also has a negative effect on the immune system and prevents the release of immunotransmitters. The hippocampus and the amygdala (= almond kernels) important parts of the limbic system, which plays a central role in emotion processing, can also modulate the adrenal axis hormone.

The vegetative (= autonomous) nervous system also plays an important role in the stress response. The activation of the sympathetic nervous system mediates the physical reactions during the "fight-flight reaction". The parasympathetic nervous system is rather active at rest. (cf. Rüegg J C, 2001)

1.4.11 Adrenaline - Adrenaline rush from the adrenal medulla

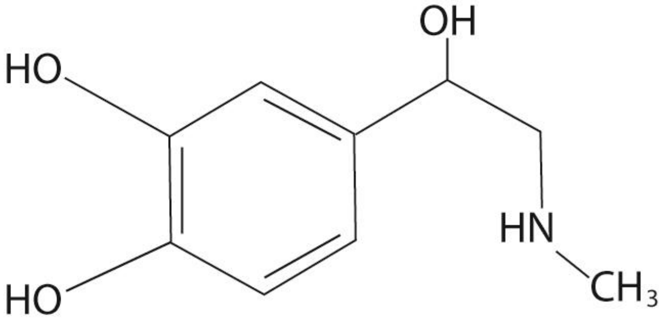

Fig. 2: Adrenaline: chemical composition of adrenaline

Qeulle: Not modified take over from, (Andrawis A, 2013).

Adrenaline and noradrenaline are important stress hormones and are produced in the adrenal medulla. Norepinephrine is also released during an adrenaline rush, but in 4 times less quantity.

Adrenaline is the most important hormone of the neurotransmitters and belongs to the group of catecholamines. The hormones noradrenalin and dopamine, which also belong to the group of catecholamines, have a similar effect. They alert the body in dangerous situations. Fear and anger occur in humans, the sympathetic nervous system is activated and the adrenaline level even rises up to ten times the value measured at rest. This activates metabolic processes.

Blood sugar is also increased by adrenaline (ibid.). Adrenaline is formed in the adrenal medulla (NNM) and in certain nerve cells (so-called sympathetic ganglia).

The blood pressure fluctuates in time with the pulse, it rises to its highest value (systolic blood pressure) for a short moment at each heartbeat, corresponding to the pressure of a 120 mm high mercury column. Finally, it falls and reaches its lowest point (diastolic blood pressure, about 80 mm Hg).

Hypertension (pathological high blood pressure) occurs when the diastolic and systolic blood pressure values exceed 90 to 140 mm Hg during a resting phase, i.e. not only during work, or 95 to 160 mm Hg in older people.

The influence of pharmaceuticals, which have an inhibitory effect on noradrenalin and adrenalin, lead to a lowering of blood pressure (ibid.).

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