Psychoneuroendocrineimmunology (PNEI)

Subjects: Endocrinology & Metabolism | Anthropology | Neurosciences

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Psychoneuroendocrineimmunology (PNEI) brings together knowledge acquired since the 1930s from endocrinology, immunology, neuroscience, and psychology. With PNEI, a model of research and interpretation of health and disease is emerging, which sees the human body as a structured and interconnected unit, where the psychological and biological systems are mutually coordinated. In the PNEI view, many factors could influence mental health, with the endocrine system involved in mediating the effects of environmental stress on mental health and inflammation in the onset and course of psychiatric disorders as a result of individual and collective conditions and behaviors. PNEI paradigm configures the possibilities of going beyond the historical and philosophical contrast between mind and body, as well as the scientific antithesis of the twentieth century, between medicine and psychology, overcoming their respective reductionism, which assigns the body to the first and the psyche to the second.

food physical activity psychiatry inflammation depression body-mind integrated care pnei paradigm stress and disease epigenetics

1. Historical background

THE INTERACTION BETWEEN THE NERVOUS AND IMMUNE SYSTEMS

Traditionally, two ideas hindered the conceptualization of neuroendocrine-immune relations. The first: the brain is an organ in itself, it is an exception, and it is not an organ like any other. In traditional physiological thinking, the brain was conceived as mainly inaccessible to the immune system. The brain is an immunologically privileged place, protected by the blood-brain barrier: this dogma, which still echoes here and there in medical congresses and some university departments, has been affected by the experiments of Hugo Besedovsky in the early 1980s and then demolished by research in the 1990s and then knocked down by the discovery of the cerebral lymphatic system in 2015.

The second conceptual obstacle can be summarized as follows: the immune system is made up of mobile and iridescent cells. How is a relationship between a highly differentiated static system and a mobile one, in perennial cellular maturation possible? The research was responsible for demonstrating first, that the immune system while being mobile and changing follows precise patterns of activation and control, and therefore it can be defined as a system and not a set of automatic and parcelled reactions; secondly, the central nervous system, although

morphologically well structured, is not static; indeed, it is incredibly dynamic not only in functional but also morphological terms, as the manual you are reading extensively demonstrates.

But these prejudices of the dualist and reductionist paradigm have not prevented scientists, curious and oriented by other ideas, to look for the experimental evidence of the connections between the great systems of physiological regulation.

The box marks the main stages of these discoveries covering the last 40 years, of which we will now see the salient points and characters.

1975-1986. Systems interface. The first tests:

- Ader and Cohen demonstrate behavioral immunosuppression in the experimental animal.
- Besedovsky shows the stimulation of the hypothalamus by immune substances.
- Study of the circumventricular organs without a blood-brain barrier.
- The study of pineal and melatonin begins.
- Felten and Bulloch demonstrate that immune cells and noradrenergic fibers are closely intertwined in the lymphoid organs.
- Blalock shows that immune cells (lymphocytes) produce pituitary hormones.
- Demonstration that IL-1 activates the hypothalamic-pituitary-adrenal (HPA) axis.

1987-1995. The paths of communication:

- In addition to HPA, it is shown that the products of the immune system influence other neuroendocrine axes.
- Neuropeptides produced by peripheral nerve fibers (substance P, CGRP, VIP) are identified. A relevant neuroimmunitary relationship is well identified, one that connects the nerve fiber (which releases CRH) to mast cells (neurogenic inflammation).
- It turns out that cytokines influence physiological functions, such as sleep, hunger, fatigue, and thermoregulation.
- The humoral and nervous connection routes are identified.
- Humoral pathways use areas with no or low barrier as input to the brain but also use an active transport system for the main cytokines (IL-1, IL-6, TNF-a). Beginning of the documentation of second-level signaling, by the induction of second messengers from the blood-brain barrier.
- The nerve pathway, mainly represented by the afferent vague, is discovered by fever scholars

1996-2021. The vision of the entire network and the study of diseases:

- Studies on cytokines and metabolism begin. It is discovered that IL-1 induces hypoglycemia with an insulin-independent mechanism. Cytokine can convey glucose to the lymphoid organs and inflamed tissues to supply energy to the hyperactive immune cells.
- Study and demonstration of cytokine production by the central nervous system.
- Demonstration that IL-1 and IL-6 play a physiological role in memory.
- Demonstration of the role that cytokines plays in the development of the embryo and the adult brain, particularly in the production of new nerve cells (neurogenesis) that is blocked by stress.
- Demonstration that metabolic (atherosclerosis, diabetes, obesity), psychiatric (depression, psychosis), neurological (Alzheimer, Parkinson), neoplastic, autoimmune, as well as behavior (sedentary lifestyle, diet) diseases are accompanied by the production of cytokines and inflammation.
- The era of diagnosis and integrated care starts.

THE PIONEERING PHASE

Those discoveries the American experimental psychologist Robert Ader and the immunophysiologist, born in Argentina and German by adoption, Hugo Besedovsky are parallel research that first demonstrated the bidirectional communication between
the central nervous system and the immune system.

Ader, in the mid-seventies, together with Nicholas Cohen, immunologist, showed that the animal brain can influence the immune system. The model they used is that of classical conditioning (also called Pavlovian). The animal that receives, together with the conditioned stimulus (sugar), an immunosuppressant, after conditioning, to the administration
of the sugar presents immunosuppression [1].

This proves, albeit indirectly that the brain has connection lines to the immune system. Besedovsky, in those years, tried to demonstrate the inverse communication; that between immunity and the brain.

And indeed in 1981, then definitively in 1986, he showed that the products of the immune system, such as interleukin-1, could activate the stress axis with the final production of cortisol[2][3].

Research showed that the brain, during infection experimentally induced in the animal, is directly informed by the immune system through inflammatory cytokines, which reach the brain and especially the hypothalamus from the periphery of the body. At the time, the identified cytokine messenger was interleukin-1 (IL-1).

The discovery of neuropeptides

The study of the analgesic effects of morphine led two neuropharmacologists, C.B. Pert and S.H. Snyder, to identify the existence of morphine receptors in the nervous tissue in 1973. Candace Pert, in the following 40 years, played a leading role in research on neuropeptides and mind-body communication in general. The research described in her book Molecules of Emotion, which has contributed to broadening the framework of communication that is not only vertical between systems, but is also horizontal and diffused to the entire body.

The neuropeptides, in fact, which are released by the fibers of the peripheral nervous tissue, or rather by the autonomic (sympathetic and parasympathetic) and the somatosensory nervous system, are the widespread communicators of the local relationships between the nervous system and immunity.

The molecular basis of bidirectional interaction between the nervous system and immunity

In the 1980s research on the molecular basis of communication between systems, taking advantage of the remarkable development that molecular immunology in those years focused on the structure of the lymphocyte membrane.

These studies showed that this fundamental class of immune cells has receptors for the essential hormones and transmitters produced by the brain.

A crucial point in this line of research is represented by an extensive written review, in 1989, by Edwin Blalock, the

physiologist at the University of Alabama, in Birmingham, USA. In this paper [4], Blalock used the tools of molecular biology to show that the immune cells have receptors for the most important products of the central nervous system and that, at the same time, these cells can produce identical or similar substances to those of the brain. Thus, the molecular basis of the bidirectional nervous system-immunity interface was demonstrated for the first time. Research of the 1990s, centered on these links, provided considerable advancement in understanding inflammatory diseases by elaborating the concept of “neurogenic inflammation” produced by the nerve.

2. The study how Psychological stress influences biological systems

Chronic stress damages the brain

The neuroendocrinology laboratory at the Rockefeller University in New York has been directed for several decades by neurobiologist Bruce McEwen, a member of the United States National Academy of Sciences (passed 2020). The main avenue of his research and that of his student and later colleague Robert Sapolsky, currently a professor at Stanford University, deals with the influence of chronic stress on the brain.

Research by the McEwen group [5] and other related groups aim to learn about the effects of chronic stress on the brain.

A series of studies, both animal and human, show that some brain areas undergo a process of neuronal loss, becoming atrophic, while in other regions the morphology of neurons changes, increase dendritic arborization and synaptic connections,

causing hypertrophy. The most important brain areas that undergo atrophy are the hippocampus and prefrontal cortices, both lateral and media. Relevant is the fact that chronic stress blocks the activity of stem cells in the hippocampus, from which it would be possible to replace lost neurons.

Therefore, neurogenesis of the hippocampus is blocked, as we have already mentioned above. The amygdala, on the other hand, becomes hypertrophic. The emotional-cognitive interweaving that accompanies and, at the same time, supports these

structural brain changes is characterized by anxiety and depression (amygdala), behavioral and executive changes (prefrontal cortices), and memory (hippocampus).

Chronic stress unbalances the immune system

Spouses Ronald Glaser and Janice Kiecolt-Glaser, immunologist and psychologist respectively, both professors at Ohio University and members of the Institute of Medicine of the National Academy of Sciences of the United States, have been carrying out varied and highly active research for years on the effects of living conditions, behaviors and emotions on the immune system.

They have studied the immune systems of people who take care of the chronically ill, such as patients with Alzheimer’s, students in exam sessions and married couples, as well as the influence of depression and social isolation, and abuse in childhood. The considerable amount of data collected, both with observational and

experimental studies shows that chronic psychic stress is a dominant factor that alters the immune dynamics, causing suppression and/or dysregulation, which can be the source of many significant diseases in which the immune system plays a central role [6].

In the following chapters, we will see the molecular biology of some of the relational dynamics that closely link emotions and immunities.

Chronic stress influences hormones and metabolism

The stress axis influences all other endocrine axes, altering growth, sexuality, thyroid activity, and metabolic activities in general. One of the scholars who has been making an all-around contribution for three decades is the Greek scientist

George Chrousos, director of the Department of Paediatrics and Head of the Endocrinology Department at the University of Athens. The scientist's prolificity can be seen in a large number of publications, the decades-long collaboration with the research programs of the American National Health Institutes, and the variety of research interests, which are all connected with a continuous thread: the study of the human being in its entirety.

His work documents that chronic hyperactivation of the stress, axis has significant repercussions even on apparently unreliable pathologies, such as metabolic disorders (dyslipidemia, hyperglycemia, diabetes, metabolic syndrome) and female fertility disorders, such as polycystic ovarian syndrome[7].

These studies have raised researchers' awareness of the centrality of stress concerning devastating epidemics, such as obesity and diabetes, occurring in all the rich countries and also in those eastern countries that are following the Western model in forced stages.

3. The study how biological systems influence the psyche

Since the 19th century, disorders and diseases of the mind have been split into neurological and psychiatric disorders and entrusted to two different medical approaches. Neurological disorders are by definition the result of brain injury and have in the last centuries achieved the *status* of true pathologies. On the other hand, psychiatric disorders have long been lost in the fog of mental symptoms without "focal brain injury". The last century has seen a shift from the domain of psychoanalytic psychiatry in the first half to the domain of biological psychiatry and psychopharmacology. The turning point in psychiatry came in the late 1970s, when the American Psychiatric Association [8], speaking through its Chairman Melvin Sabshin, launched into a "vigorous effort to re-medicalize Psychiatry" fighting on two fronts: against the historic power of psychoanalysis and the fledgling mortal threat represented by anti-psychiatry [9]. With the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), published in 1980, a complete adherence of Psychiatry to the biomedical model is achieved. The psychiatric identity crisis seemed to be definitively resolved. In fact, after two decades of apparent triumph, the crisis has reappeared.

Gardner C, Kleinman A. on *New England Journal of Medicine* wrote: "Biologic psychiatry has far failed to produce a comprehensive theoretical model of any major psychiatric disorder, any tests that can be used in a clinic to

diagnose clearly defined major psychiatric disorders, or any guiding principle for somatic treatments to replace the empirical use of medications"[10].

The promises of biological psychiatry, based on the extensive and punctual use of psychotropic drugs, have been broken on the rocks of controlled empirical research that has documented the not sufficiently effectiveness of the chemical molecules proposed in the last 50 years in the face of significant adverse effects on numerous systems including the central nervous system if used beyond the necessary time[11] also of selected birth deficits as in the case of the use of antidepressants during pregnancy [12].

Of course, "biologic knowledge is foundational to good psychiatry", but what biology? Human biology is modulated by mental activity. The in vivo investigation of the human brain, through brain-imaging, has shown that psychological interventions have effects on the function and anatomical structure of brain circuits. In addition, the epigenetic investigation has further demonstrated that psychological and body-mind interventions induce changes in gene expression coding for brain receptors and neurotransmitters, thus providing a way of scientific explanation on the mechanisms of action of effective psychological interventions in the treatment of mental disorders [13][14]At the same time, nutrition and physical activity play a significant role in the modulation of mental and emotional states. The evidence of effectiveness is now numerous, as shown by studies describing advantages from the administration of certain nutrients as augmentation therapies, and the good effects of physical activities on brain plasticity and epigenetics [15][16][17] Ignoring these pieces of evidence is no longer possible for those who deal with mental health, both as a single professional and as a dedicated health facility.

The PNEI model of health and disease sees the human body as a complex and interconnected unit, where the psychological and biological systems are mutually coordinated. The new integrated approaches provide the theoretical and practical basis to the prevention and treatment of non-communicable diseases, those of competence of both internists and psychiatrists; likewise, allow to go beyond the historical-philosophical contrast between mind and body, and overcome the twentieth-century scientific reductionism which assigns the body to the medicine and the psyche to the psychology.

4. A New Psychopathological Model

Biology is undergoing an exciting moment, at present underway, bridging the abyss that has separated the area of human biology from that of social history. The biological sciences are the driving force of a landmark revolution. The reductionist and determinist framework has given way to a new vision that no longer sees the genome as a headquarters imparting instructions to the organism, but rather as an adaptive device that responds to environmental requirements by regulating gene expression. Epigenetics is a rapidly expanding science that researches molecular mechanisms through which the environment and individual life act based on the information contained in the genome. These new lines of research clarify the relations existing among the very early stages of life, starting from conception, and the health of the child and adult[18]. They offer us an explanation of the molecular mechanisms, stress-related and inflammation-based, with which characteristic features influence our mental health (pollution, diet, sedentary lifestyle, stress, social position, gender).

Mental balance can be influenced by a variety of factors: endogenous and biological, such as the microbiota and the immune system[19], environmental, such as exposure to environmental pollution[20]; behavioral, such as nutrition[21]and sedentary lifestyle[22][23], social status[24][25].

In this view, the endocrine system plays a pivotal role in mediating the effect of environmental stress on the health of individuals through direct effects[26] and epigenetic modifications[27]

In short, it is possible to bring to the horizon of contemporary medicine the evaluation of the individual as a whole (see **Figure 1** showing depression as an example).

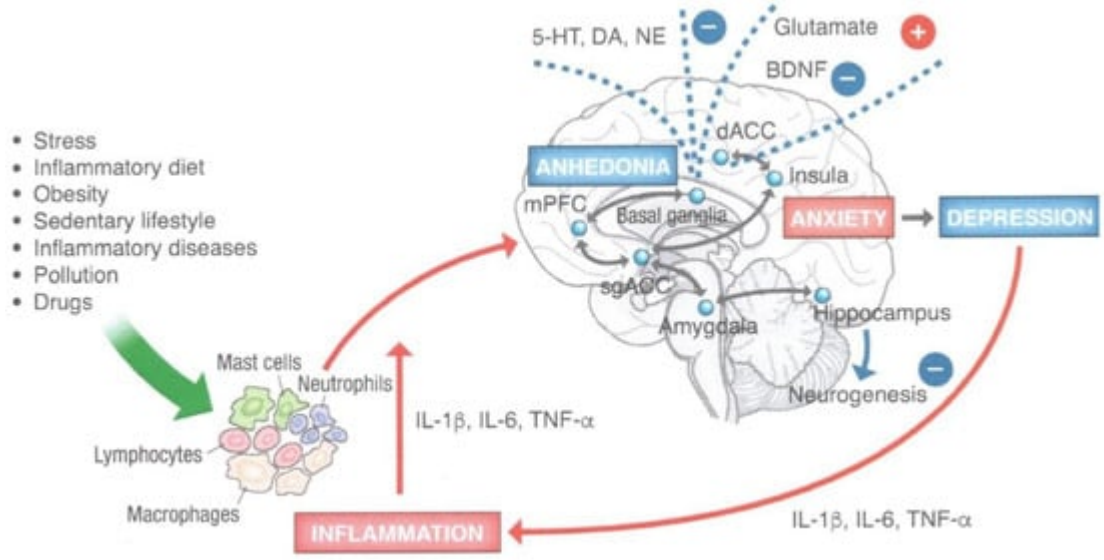

Figure 1. The bidirectional relationship between depression and inflammation. The image illustrates the inflammatory effects of several factors, starting with stress. The release of inflammatory cytokines by immune cells alters the metabolism of fundamental neurotransmitters such as serotonin, norepinephrine, dopamine, BDNF, and glutamate, reducing the first four levels and increasing those of the last. These alterations negatively affect the activity of strategic brain areas and their mutual connections. There are psychological consequences, with the inability to experience pleasure (anhedonia), anxiety, depression, and poor self-esteem; and biological, with alterations in the medial prefrontal cortex, the anterior cingulate cortex, the basal ganglia, the amygdala, the hippocampus, and the insula. 5-HT = serotonin; BDNF = brain-derived nerve factor; DA = dopamine; dACC = dorsal anterior cingulate cortex; mPFC = medial prefrontal cortex; NE = norepinephrine; sgACC = subgenual anterior cingulate cortex. Reprinted with permission from: F. Bottaccioli, A.G. and Bottaccioli (2020). Copyright 2020 Edra.

5. Stress Management and Psychological Interventions

Stress is a physiological response of the organism, multisystemic and integrated, to any need: of a biological nature (e.g., viral infection), and mental nature (emotional and/or cognitive). A response that in the short term (acute stress) promotes dynamic phenomena of adaptation of the organism to the most varied environmental

conditions but which, if it occurs too frequently and/or for long periods (chronic stress), and most importantly, if the stress is beyond our ability to control (coping), can have long-lasting dysfunctional effects on different biological systems (nervous, immune, endocrine and metabolic) and pathological consequences on various organs and systems (allostatic load)[28].

Prolonged stress leads to hypotrophy and reduced activity of the Prefrontal Cortex, a key brain structure implied in working memory, context appraisal, executive, and self-regulatory functions. Hippocampus, which is crucial for memory, mood, and Hypothalamus-Hypophysis-Adrenal (HPA) axis regulation, can be injured by chronic stress via cortisol exposure[29] Moreover, multiple adverse events during lifespan correlate with the reduction of many brain areas involved in emotions regulation, like the medial prefrontal cortex, anterior cingulate cortex, and insular cortex. These morphological and functional changes in neural circuits enhance long-term risks for psychopathology occurrence, in particular depression, anxiety, post-traumatic stress disorder (PTSD), and addiction[30]. Research on the neurobiology of psychiatric diseases evidences structural remodeling of the hippocampus and PFC, as well as clinical conditions characterized by chronic stress often associated with cognitive deficits, dysregulated cortisol secretion, altered metabolic signals, and immune imbalance which finally result in inflammation[31]. Epigenetics is regarded as a molecular pathway mediating chronic stress's transduction into multiple potential gene expression patterns[32]. Epigenetic signature of HPA axis, namely the gene coding for the glucocorticoid receptor (*NR3C1*), as well as the signature gene coding NFkB, main inflammatory intracellular pathway, and other signature genes related to neurotransmitters (serotonin, GABA) and neurohormone (oxytocin), neuropeptide (BDNF), enzyme (mono-amino-oxidase A, MAO-A), it is thought to be some of the molecular mechanism underlying the pathogenesis of the psychiatric disorder.

When psychological and mind-body interventions work, it not only improves the mental state and well-being of the person but changes the epigenetic signatures[33]. It has been deeply described the mechanistic pathways involved in epigenetic reversion of HPA axis activity and in the down-regulation of inflammatory transcriptional response (mainly via NF-kB) that underpin the ability to respond effectively to stress, thus improving resilience and clinical and biological recovery of both mood and immunity balance [34]. It has been demonstrated reduced methylation of the BDNF gene, thus leading to enhanced gene expression, in patients with eating disorders who undergo behavioral therapy sessions, and this correlated with clinical improvement of specific symptoms. In patients with PTSD, Prolonged Exposure Therapy (PET) leads to neurobiological responses which can be measured through epigenetic modifications in key stress-related genes. In fact, in greater responders to psychotherapy intervention, there is a significant reduction in methylation of the GR gene (NR3C1) that directly correlates with higher baseline levels of cortisol (frequently low in PTSD), and a decrease in cortisol reactivity under stress tasks[35][36].

A growing body of research has investigated the effects of mind-body therapies (MBTs), like meditation, tai chi, qi gong, yoga, on biological markers of mind inflammation. A seminal review by Bower and Irwin [37] which have included 26 trials, confirmed the anti-inflammatory effects of MBTs on circulating markers of inflammation, such as c-reactive protein (CRP). Two controlled studies PNEIMED (Meditation Psychoneuroendocrineimmunology-based), in healthy middle-aged and young volunteers, showed a reduction of salivary cortisol under basal and stressful conditions [38][39].

New Frontiers

A new phase in PNEI research has begun, that of innovation in diagnosis and treatment. Innovation whose keyword is integration.Integration above all within biomedicine and psychology, among their numerous and often incommunicable specializations and “schools”. And then between the biomedical sciences and psychological sciences [40], experimenting with

diagnostic tools that aim to capture the unbalanced factors of a person in their entirety, thus investigating both the psychological and the biological dimensions. Only new and more efficient diagnostic tools, in fact, can provide the basis for a treatment approach, which consists of prevention and therapy, to make it truly integrated and to provide qualified advice on lifestyles, which are then the primary determinants of health, to offer a treatment program that works on both the psychic

and the biological dimensions, to guarantee the use of therapeutic devices not restricted to synthetic pharmacology[41].

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