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Psychoneuroendocrineimmunology (PNEI) and longevity

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Psychoneuroendocrineimmunology (PNEI) is the science which studies the interactions between psychological, neural, endocrine and immunological processes.

The concept of the PNEI system was developed in the seventies and eighties through the discoveries of the interaction between immune system and molecules with neuroendocrine activity targeting multiple organs; the interdependence between immunological, psychological and neuroendocrine mechanisms has been elucidated through several studies subsequently.

PNEI system is a self-regulation network which is involved in the homeostasis of the organisms, in the maintenance of chemical-physical-neuropsychological balance in response to stimuli of various nature.

The present review provides an overview of the fundamental scientific literature on PNEI and its interaction with chronic low grade cellular inflammation processes and consequently with longevity. Similarly literature data on the strict link between hormetic processes and PNEI system are discussed, with reference to resilience as a key-factor in the natural/pathologic evolution of aging.

Keywords: PNEI, Psychoneuroendocrineimmunology, Psychoneuroimmunology, Longevity, Hormesis, Inflammation, Polyphenols

Introduction

Psychoneuroendocrineimmunology (PNEI) is the scientific discipline which studies the interactions between psychological, neural, endocrine and immunological processes.

The concept of the PNEI system was born in the second half of 20th century and developed mainly in the seventies and eighties when different experiments confirmed the existence of a network of immune-neuro-endocrine interactions [1]. In the nineties Ader [2] diffused the main concepts of PNEI to a wider audience, following the discovery that the lymphocytes (immunological cells) produce TSH (hypophyseal hormone) and other molecules with neuroendocrine activity. The scientific confirmation about the interdependent relationship between immunological and neuroendocrine mechanisms has progressively led to a new reappraisal of diagnostic and therapeutic pathways in several medical fields and namely in longevity medicine.

From the morpho-functional point of view PNEI system includes the (patho-) physiological mechanisms proper of human psyche, neurological system (limbic system and namely hypothalamus in primis), endocrine system (e.g. hypophysis and receptor glands) and immunitary system. These organs/circuits are part of an integrated self-regulation network that aims at psycho-somatic homeostasis in response to endogenous and exogenous stimuli of various nature (**Figure 1**).

In this paper an overview of a few scientific evidences and of most significant literature data about PNEI and longevity are presented.

In the latest years medicine is adapting the concept of illness

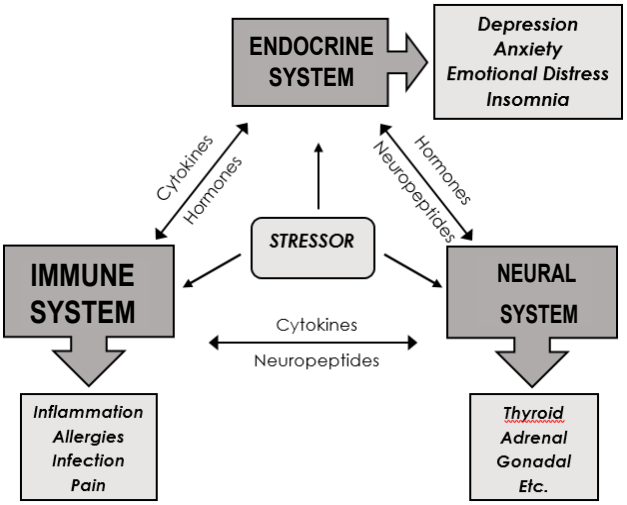

Figure 1. PNEI: Interconnections and signaling among psyche, neural, endocrine and immune systems.

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and its modus operandi based on it. Emotions, mental attitude, lifestyle, social support, nutrition are increasingly recognized as key elements in the processes of diagnosis and treatment of any disease. The functioning of the PNEI system highlights how psycho-social elements are not only abstract expressions of a subjective experience; their value is also expressed through concrete patho-physiological clinical manifestations that depend on the individual-environment relationship.

Literature evidence has highlighted how chronic low grade cellular inflammation (CLGCI), neurodegenerative and cardiovascular disorders, obesity, diabetes, cancer and, more generally, senescence are all processes which are strictly linked to PNEI system activity. More recently a fundamental link between hormetic processes and PNEI system have been shown as well, referring to resilience as a key-factor in the natural/pathologic process of aging [3].

In 2009 an editorial in the Lancet [4], titled "What is health? The ability to adapt", it is clearly stated that health is not a state of complete physical, mental, and social well-being; and nor is it merely the absence of disease or infirmity". More properly the authors, following Georges Canguilhem's ideas, state that "health is the ability to adapt to one's environment. Health is not a fixed entity. It varies for every individual, depending on their circumstances" and they appreciate "the beauty of Canguilhem's definition of health-of normality-which includes the animate and inanimate environment, as well as the physical, mental, and social dimensions of human life". According to this more comprehensive and modern view of health, PNEI system in fact is recognized to play a significant role in aging processes [5]. The imbalance between emotional and physical stimuli is definitely connected to an ongoing series of phenomena that include and affect biological, psychological and social aspects within human life.

A literature search concerning PNEI system and longevity has been performed through various biomedical databases, such as pubmed/medline, google scholar, embase. The terms, PNEI, Psychoneuroendocrineimmunology, psychoneuroimmunology, psychosocial, resilience, mood, hormesis, together with the terms longevity and aging were used for article search. As this paper was not intended as a systematic review, after screening a few hundreds of the resulting abstracts, the full texts of the most pertinent articles have been collected, reviewed and lastly discussed and included as references in the present text.

Our main aim was to highlight the main concepts and evidences about the possible role of PNEI system in several medical fields, namely in the inflammaging process, in the longevity mechanisms, as well as in the "innovative" hormetic approach.

PNEI and Inflammation

PNEI primarily provides the biological basis of bidirectional communication between the endocrine, immune and neuropsychological networks in physiological and pathological conditions. Psycho-emotional and affective state of the individual human being seem to influence or modify the course of a pathological organic event [6].

The pivotal process through which the PNEI system intervenes in most diseases is undoubtedly inflammation [7,8], in terms of interactions with the CLGCI which accompanies human life. **Table 1** summarizes the main literature evidence regarding PNEI and inflammation, as reported in this section.

Chronic stress, also called distress, basically represents the persistent disequilibrium of the PNEI system pillars, and it acts on the hypothalamus-hypophysis axis and the whole endocrine system, which results finally in a modification of cortisol level. Stress consequently favors inflammation of the tissues due to the increase of cortisolemia and the increase of inflammatory cytokines (i.e. IL-1, TNF, IL-6); they activate the immunitary system in a pro-inflammatory sense. Extensive innervation of lymphoid organs by neurovegetative fibers, releasing especially norepinephrine, acetylcholine and neuropeptides has been widely documented [9].

An important role is played by the plexuses of sympathetic nerve fibers that surround the arterial vessels which penetrate the lymphoid organs. The interaction occurs by means of all immune cells, especially those of innate immunity, which are typically involved in inflammation processes. Among them mast cells are known to be able to release large amounts of histamine and other active substances that cause vasodilation and subsequently inflammation. Of interest, these cells are present not only under the skin and the mucous membranes of the body, but also in fundamental organs, including the brain, where they can produce inflammation as well [10].

Mast cells can be activated in an inflammatory sense by the main neuropeptides (Calcitonin-gene-related-peptide, substance P, neuropeptide Y, nerve growth factor, vasoactive intestine peptide), as well as by adrenaline, noradrenaline and other substances released by nerve fibers [11]. It is clear how the vegetative nervous system is able to modulate the inflammatory processes by interacting with the mast cells and other relevant immune system components.

In the last half century inflammation has been recognized as one of the main (if the not the main) causal processes in atherosclerosis and in lipid profile alterations [12]. CLGCI and hyperdyslipidemia may be connected to several causal and favoring factors and for example the correlation between psychic depression, chronic stress and alterations in the blood fat profile (dyslipidemia) has long been known in medicine [13-16].

PNEI system science describes how all the compartments influence and are influenced by the inflammatory processes: in fact also the immune system is affected by the alterations related to depression and dyslipidemia. Dantzer and coll. suggest that through the release of cytokines in the brain an inflammatory condition is established and it results in neuronal activity alteration which causes depression and a procession of symptoms summarized in a framework called "sickness behaviour" [17,18].

This close inter-relationship of inflammation, depression, dyslipidemia and metabolic alterations is increasingly being investigated to understand the pathogenesis of cardiovascular and cerebrovascular diseases, but also to justify the differences recorded, notwithstanding the same pharmacological treatment, in the post-operative course of patients who have suffered myocardial or cerebral infarction. An increasing number of studies [19] is equating the weight of the risk factors related to psychosocial negative situations (depression, anxiety, hostility, social isolation) to the classical biological ones (smoking, hypercholesterolemia, hypertension, obesity, diabetes) within the pathogenesis of cardiovascular diseases [20-22].

Chronic stress and inflammation are factors that can also increase the risk of cancer and metastasis, particularly in the lymphoglandular system. Dealing with the details of the molecular mechanisms underlying this correlation is beyond the scope of this work. The most reliable hypothesis is that an increase in the production of neuropeptides and stress hormones can cause on one hand an alteration in the signaling of cell proliferation (i.e. MTOR/autophagy pathways), and on the other side the increase in cortisol, with consequent dysregulation of immune response, insulin and leptin.

Knowing the link between the neuroendocrine, the psychological

Table 1

PNEI and Inflammation: Main literature data

Authors – year	Topic	Outcomes
Vitetta et al. [6]	Mind-body medicine: stress and its impact on overall health and longevity	Adverse health outcomes such as coronary heart disease, gastrointestinal distress, and cancer have been linked to unresolved lifestyle stresses, expression of a negative impact on human life span.
Wirtz et al. [7]	Psychological Stress, Inflammation, and Coronary Heart Disease	Chronic stress increases the risk of incident coronary heart disease and poor cardiovascular prognosis; acute emotional stress can trigger acute events in vulnerable patients. Stress also increases inflammatory markers.
Alcocer-Gómez et al. [8]	Stress-Induced NLRP3 Inflammasome in Human Diseases	Stress can trigger inappropriate activation of the NLRP3 inflammasome which contributes to the onset and progression of age-related diseases such as metabolic disorders and metabolic syndrome.
Bellinger et al. [9]	Sympathetic Modulation of Immunity: Relevance to Disease	Sympathetic innervation of lymphoid tissues meets the criteria for neurotransmission with immune cells as target cells
Rosa et al. [11]	The role of histamine in neurogenic inflammation	The inflammatory response evoked by the activation of the sensory nerve fibers is brought about by neuropeptides released from the peripheral endings of sensory neurons upon their stimulation.
Capron [12]	Inflammation and atherosclerosis	Human atherosclerotic lesions share many features of an inflammatory reaction of arterial intima (increased penetration of plasma components, proliferation of smooth muscle cells, infiltration by monocytes/macrophages and lymphocytes).
Yu et al. [13]	Psychological factors and subclinical atherosclerosis in postmenopausal Chinese women in Hong Kong	High perceived stress scores in postmenopausal women were associated with an increased risk of elevated total cholesterol and elevated low-density lipoprotein cholesterol.
Fan et al. [14]	Association between job stress and blood lipids among university staff in Yunnan province	Male staffs with higher job stress had higher risk of increased serum triglycerides (3.5 folds) and increased serum low density lipoprotein-cholesterol (2.9 folds). The risk of elevated serum triglycerides increased in proportion to increasing job stress.
Xu et al. [15]	Association between job stress and newly detected combined dyslipidemia among Chinese workers: findings from the SHISO study	Effort, over-commitment, low reward and effort-reward imbalance increase the risk of dyslipidemia, especially triglycerides and LDL-cholesterol.
Neves et al. [16]	Chronic stress, but not hypercaloric diet, impairs vascular function in rats	Stressed rats presented higher concentration of insulin, corticosterone, lipids and higher atherogenic index values. Stress increased intima-media thickness.
Dantzer et al. [17]	From inflammation to sickness and depression: when the immune system subjugates the brain	Conditions of chronic inflammation exacerbate the sickness and depression-like behaviors.
Dantzer et. Al. [18]	Inflammation-associated depression: from serotonin to kynurenine	Inflammation-associated depression: the degradation of tryptophan induces the synthesis of kynurenine (neurotoxic compound).
Rozanski et al. [19]	Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy	Chronic psychosocial stress can lead, probably *via* excessive sympathetic nervous system activation, to exacerbation of coronary artery atherosclerosis.
Rozanski et. al. [20]	The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology	Both exercise and multifactorial cardiac rehabilitation with psychosocial interventions have demonstrated a reduction in cardiac events. Psychopharmacologic interventions may also be effective.
Yusuf et al. [21]	Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study	Smoking, raised ApoB/ApoA1 ratio, history of hypertension, diabetes, abdominal obesity, psychosocial factors, lack of daily consumption of fruits and, regular alcohol, lack of regular physical activity, were all significantly related to acute myocardial infarction.
Halaris [22]	Inflammation, heart disease, and depression	Morbidity and mortality of cardiovascular disease is possibly linked to mental stress which leads to sustained sympathetic overdrive and diminished vagal tone, contributing to a pro-inflammatory status.
Chida et. al. [23]	Do stress-related psychosocial factors contribute to cancer incidence and survival?	Stress-prone personality or unfavorable coping styles and negative emotional responses or poor quality of life were related to higher cancer incidence, poorer cancer survival and higher cancer mortality.

and the immune system, it is not surprising that a meta-analysis carried out on 165 controlled studies in oncology concludes that psycho-social distress is related to an increase in the incidence of cancer, a worse prognosis and an increase in mortality [23].

All these studies show how psychological emotions and stress can translate into an inflammatory process that bidirectionally involves the entire PNEI system and the target organs.

PNEI and Longevity

The PNEI approach is being investigated and proposed to

address complex and multifactorial processes such as healthy aging and longevity [5]. Chronic inflammation is considered the common ground of many pathogenetic processes and in the early 2000s Franceschi called "inflammaging" the combination of CLGCI, as core pattern of any chronic degenerative process and senescence [24]. Inflammatory processes can originate and worsen due to multiple causes, both of organic and of psychological/social nature, hence a close interdependence and connection between inflammaging and PNEI system dysregulation has been highlighted [25].

Looking at the interaction between PNEI and psycho-physical aging several studies have been published. One study has shown that a positive childhood from the psychosocial point of view may guarantee a better cardiovascular function [26]; similarly a Korean study on the psychosocial factors which interfere on healthy aging showed that depression is the most relevant one, whereas conversely the perceived health status, ego integrity, self-achievement, self-esteem, participation at leisure activities were beneficial factors [27].

Another study has pointed out that senescence is a process that can be improved by self-estimation and self-perception of own aging with an increase of 7.5 years in the lifespan, in comparison to the subjects who negatively interpret their aging process [28]; and this result was achieved regardless of economic-social status, gender, loneliness and disability.

Through a huge cohort of 3966 homozygous twins aged 70 years or older, who were followed for a mean period of 9 years [29], other authors showed that the individual level of feeling of well-being predicted a greater longevity, regardless of family, genetic and shared environment factors.

One of the most pertinent and relevant prospective investigation on long-term aging and its connection with biological and psycho-social factors was led by Vaillant and subsequently by Waldinger ("The Harvard Grant study") and it was extended for about 75 years [30]. The great amount of collected data regarded 268 physically and mentally healthy Harvard college students. These subjects were males of American nationality with a high social status; the information prospectively collected on a regular basis concerned: a) the physical and mental state, b) several possible risk factors (i.e. smoke habit, alcohol consumption), c) psycho-social features such as the enjoyment of a career, the experience of retirement and the quality of family life. The purpose of the study was to identify biological/psycho-social predictive factors of healthy aging. The Harvard grant study, unique for duration and typology of investigated subjects ("high social class") highlighted a few relevant findings: a) alcoholism was the factor with the most destructive power, strongly correlating with neurosis and depression, b) smoking was the second factor contributing to early morbidity and death, c) financial success depended on warmth in human relationships and, beyond a certain level, not on subjects' intelligence, d) the human warmth of the relationship mother-child positively influenced the rest of life, e) the higher warmth of the relationship in childhood with fathers correlated with lower rates of anxiety for adults and greater "satisfaction of life" at the age 75. The fundamental conclusion of this study showed that the warmth of human relationships has the greatest positive impact on 'life-span and satisfaction'.

This confirmation of the significant role of PNEI system in longevity has been regarded as a basic fact to be taken into consideration in any medical/social approach towards healthy-aging.

Telomere length is another recognized important longevity index and furthermore it is negatively influenced by chronic stress and depression [31]. A clinical study [32] examined 58 young women (38 years on average), of whom 39 were mothers of chronically ill children (and therefore in a prolonged stress condition), while the remaining ones served as a control group. All women were evaluated with psychological tests of stress measurement and biological tests, including telomere length measurement, telomerase activity, and cellular oxidative stress. The resulting findings showed that chronic stress in the mothers of sick children was associated with lower telomerase activity, lower telomere length and greater cellular oxidative stress. Conversely in the same study the subjects practicing meditation (mindfulness) had greater telomerase activation and longer telomeres.

Epigenetic changes related to chronic stress were highlighted furthermore in a study on pregnant women suffering from chronic stress; in this study the authors demonstrated that also the telomeres of the offspring are affected, which will be statistically shorter both for infants and adults [33].

Another study conducted on infants in early childhood, showed a strong difference in telomere length linked to their psychological and behavioral state [34]. The group of children characterized by greater emotional reactivity, measured by psychological tests, increased cortisol and heart rate, and also showed a reduction in telomere length in cells [35].

Oxidative stress has been recognized at the base of many aging processes and similarly the linkage between mood and neuronal diseases, immunosenescence and oxidative stress has been shown in different studies [36-38].

This growing evidence about the inter-relationship between PNEI pathways, CLGCI and aging science (**Table 2**) highlights the relevant correlation between the negative psycho-emotional factors and social chronic stress and ultimately a worse longevity and a lower quality of the aging processes.

Table 2

PNEI and longevity: Pertinent literature

Authors - year	Topics	Outcomes
Guidi et al. [5]	Psychoneuro-immunology and Aging	The neuroendocrine mechanisms of psychoimmune interaction: chronic psychological distress and depression may worsen some immune functions in the aging process.
Franceschi et al. [24]	The network and the remodeling theories of aging: historical background and new perspectives	Two general theories on aging, as well as their experimental basis and data, suggest that aging and longevity are related, in a complex way, to the capability to cope with a variety of stressors.
Fougère et al. [25]	Chronic Inflammation: Accelerator of Biological Aging	Biological aging is characterized by a chronic low-grade inflammation level. Inflammaging effects include oxidative stress, mitochondrial dysfunction, glycation, deregulation of the immune system, hormonal changes, epigenetic modifications, and dysfunction of telomeres.

Appleton et al. [26]	A prospective study of positive early-life psychosocial factors and favorable cardiovascular risk in adulthood	Higher levels of childhood attention regulation capacity, cognitive ability and positive home environment were associated with healthy levels of blood pressure, cholesterol, and BMI.
Han et al. [27]	Psychosocial factors for influencing healthy aging in adults in Korea	The factors that significantly influenced healthy aging were depression, participation in leisure activities, perceived health status, ego integrity, self-achievement and self-esteem.
Levy et al. [28]	Longevity increased by positive self-perceptions of aging	Self-perceptions of aging had a greater impact on survival than did gender, socioeconomic status, loneliness, and functional health.
Sadler et al. [29]	Subjective wellbeing and longevity: a co-twin control study	The association between subjective well-being and longevity is independent of familial factors such as shared genes and common environment: there is a causal link between subjective well-being and longer lifespan.
Epel et al. [31]	Can meditation slow rate of cellular aging? Cognitive stress, mindfulness, and telomeres	Meditative practices appear to improve the endocrine balance (high DHEA, lower cortisol) and decrease oxidative stress. Thus, meditation practices may promote cell longevity and protect the telomeres.
Epel et al. [32]	Accelerated telomere shortening in response to life stress	In healthy women, psychological stress is associated with indicators of accelerated cellular and organismal aging: oxidative stress, telomere length, and telomerase activity.
Entringer et al. [33]	Stress exposure in intrauterine life is associated with shorter telomere length in young adulthood	Exposure to maternal psychosocial stress during intrauterine life is associated with significantly shorter telomere length in young adulthood. The prenatally stressed individuals also exhibited insulin and leptin resistance, higher BMI, alterations in the regulation of the hypothalamic–pituitary–adrenal axis.
Entringer et al. [34]	Maternal psychosocial stress during pregnancy is associated with newborn leukocyte telomere length	As to the effects of potential determinants of newborn leukocyte telomere length (gestational age at birth, weight, sex, and exposure to antepartum obstetric complications), a significant, independent, linear effect of pregnancy-specific stress on newborn telomere length was shown.
Kroenke et al. [35]	Autonomic and adrenocortical reactivity and buccal cell telomere length in kindergarten children	Children with the combination of higher sympathetic reactivity, greater parasympathetic withdrawal, and higher cortisol response to an acute stressor had the shortest telomere length.
Ng et al. [36]	Oxidative stress in psychiatric disorders: evidence base and therapeutic implications	Oxidative stress may be a common pathogenic mechanism underlying many major psychiatric disorders. Multi-dimensional data support the role of oxidative stress in schizophrenia, depression, bipolar disorder and anxiety disorders.
De La Fuente [37]	Role of Neuroimmunomodulation in Aging	With aging, the immune cells show an increase in oxidant and inflammatory compounds and a decrease in antioxidant defenses, which is more evident in phagocytic cells. The main mechanism is the activation of NF-kB in the leukocytes.
Vida et al. [38]	Increase of Oxidation and Inflammation in Nervous and Immune Systems with Aging and Anxiety	Animals with poor response to stress and high levels of anxiety had high levels of oxidative stress in immune cells and showed premature immunosenescence and shorter life expectancy.

Therapeutic Approaches to Improve PNEI System

A lot of possible procedures which may positively act on the PNEI system have been described and the main ones are related to the techniques aimed at stress management such as: slow breathing (i.e. 6 breaths/minute) [39,40], contra-resistance respiratory training [41], meditation [42], prayer [43,44], autogenic training [45]. **Table 3** reports a few of the most validated methods and procedures which may have a role in PNEI management within longevity medicine.

It has been shown that carotid baroceptors are influenced by most of the stress management methods as to above [46], with a particular reduction in blood pressure and heart rate, achieving the cerebral alpha state of vigilant relaxation and basically a reduction of excess cortisol. Other physical activities useful in PNEI system adaptation are exercising, dance, Yoga and Tai-Chi.

Meditation, mindfulness and other spiritual/religious practices have been documented as useful ways to improve PNEI system functionality; studies on particularly long-lived subjects in Spain, Italy and Greece have shown how the regular exercise of meditative/spiritual practice correlates with a greater telomere length and a decidedly long life expectancy [28,31]. In fact multiple biological factors may have jeopardized the final results of these studies, hence a multifactorial analysis would be of help in future similar studies.

PNEI-orientated approaches basically aim at increasing resilience, which generally expresses the ability of a system to adapt to changes. In psychology resilience is the ability to successfully adapt to life tasks in the face of social disadvantage or other highly adverse conditions [47].

All living beings may have a variable degree of self-repair (possibly returning to the original condition) after a negative change of their primary state. High level of personal resilience is a basic target in longevity medicine [3] and improving PNEI mechanisms in the elderly leads to an increase of their resilience, as well as to a higher psycho-physical balance [48].

Autonomic neural system plays a major role in several aging processes; heart rate variability, which is the result of vagus and sympathetic nerve interaction, is a recognised expression of the major (higher variability) or minor (lower variability) resilience and, to some extent, of PNEI functionality [49,50].

The vagus nerve connects the brain to the internal organs and it accounts for 75% of all parasympathetic nerve fibers. In 2002, a large review showed for the first time the evidence on the anti-inflammatory role of this nerve pathway [51]. In 2003, an Italian study showed that stimulation of the vagus nerve has a powerful anti-inflammatory effect, evidenced by the reduction of TNF-alpha,

Table 3

PNEI-targeting procedures and methods related to longevity medicine

Therapeutic treatment	Physiological effects	Related bibliography
Slow breathing	Carotid baroceptors regulation; blood pressure and heart rate reduction; excess cortisol reduction	39,40,41,45,46,49,50
Contra-resistance respiratory training	Carotid baroceptors regulation; blood pressure and heart rate reduction; resilience improvement	46,49,50
Meditation	Carotid baroceptors regulation; blood pressure and heart rate reduction; excess cortisol reduction; correlation with greater telomere length and long life expectancy; resilience improvement	42,45,47,48,49,50
Prayer	Carotid baroceptors regulation; blood pressure and heart rate reduction; excess cortisol reduction; resilience improvement	43,44,47,48,49,50
Autogenic training	Carotid baroceptors regulation; blood pressure and heart rate reduction; excess cortisol reduction; resilience improvement	39,47,48,49,50
Vagus nerve stimulation (neural therapy, acupuncture, massages)	Peripheral inflammation regulation; TNF-alpha reduction	51,52,53,54,55
Nutrition and nutraceuticals (polyphenols, omega 3 fatty acids)	Oxidative stress reduction; anti-inflammatory pathways activation; hormetic processes activators; protection against cognitive decay and mood alterations	47,48,56,57,58,59,60,61,62,63,64,65
Melatonin supplementation	Sleep-wake cycle regulation; cerebral and immuno-endocrine metabolism support; chronic stress control (cortisol)	66,67,68

one of the most important inflammatory cytokines [52]. Further studies [53,54] suggest that modulation of the whole neurovegetative system is able to regulate peripheral inflammation. Manipulating the vagus and the neurovegetative system (e.g. with neural therapy, acupuncture, massages) [55] can therefore represent a key strategy to be combined with more traditional treatments, in order to combat inflammatory processes of various kinds.

In Okinawa, Japan, an important study was performed to understand the reasons of the longer and healthier lifespan typical of the local population. The main factors involved in subjects' healthy aging were: a) the diet rich omega 3 fatty acids and in polyphenols, which are known to have a role in psycho-neural disorders [56-58], b) the good level of physical activity, but also c) the positive and compassionate way of thinking and of living one's aging [57].

Nutrition is another decisive factor in counteracting inflammation, and it may represent one of the first therapeutic interventions in PNEI system as well. The conventional western diet that is being followed in recent decades, is leading to a worsening of immune system, hence to the early development of a number of diseases such as diabetes and autoimmune diseases, characterized by chronic inflammation processes. Stress-diet-microbiota-mood relationship has been widely investigated [59,60] and evidences definitely point at the gut-brain axis as the core issue which links nutrition to PNEI pathways.

As for the use of nutraceuticals/food supplements, scientific data are increasingly demonstrating their contribution to body successful aging and to PNEI system improved function [56-58,61,62]. Polyphenols represent the most interesting and well documented natural antioxidants which help combating the excess of free radicals and aging degenerative processes [62].

Polyphenols such as maqui, hydroxytyrosol, amla, curcumin, all of them recognized as powerful antioxidants, have shown good potential in several studies as to the decrease of oxidative stress. Interestingly polyphenols' role as hormetins [63] has been recognized as well, hence they may stimulate a beneficial hormetic response to their ingestion. Polyphenols work also as activators of vitagenes and anti-inflammatory pathways, while their positive action in mood alterations and PNEI system has been proven more recently furthermore [56,64].

Omega 3 fatty acids may similarly be of interest in PNEI thanks to their action on mood expressions, cognitive decay, resilience as a whole [58,65].

With regards to other substances which have shown a positive influence on PNEI system, melatonin has gained popularity in the last decades, through several authoritative studies; melatonin is a hormone produced mainly by the epiphysis at night, which acts as a regulator for the complex mechanism of sleep-wake cycle, for cerebral and immuno-endocrine metabolism and for the control of chronic stress (cortisol). This multi-target hormone has been recognized as a possible anti-aging agent as well [66].

In presence of melatonin release, cortisol levels decrease: this is particularly important especially in elderly subjects, who have a significantly reduced melatonin production [66,67]. Increasing the level of melatonin through adequate sleep and (over the fifties) through dietary supplements, can be therefore a further possible support strategy which may improve mood, rebalance PNEI system and control cortisol-mediated chronic stress [66-69].

PNEI: A Hormesis-Based System

The term hormesis comes from the Greek "stimulate" and it was used for the first time in 1943 by Southam and Erhlich to indicate a specific dose/response relationship. Hormesis is a highly conserved phenomenon in the functioning evolution of animal/vegetal organisms, characterized by a dose-dependent biphasic response. The same hormetic stimulus (be it a biochemical substance, a physical stress, or a psychological event) at low doses causes a beneficial stimulation of metabolic pathways, whereas at high doses it generates a negative effect on the metabolic processes [70].

PNEI system in fact responds to hormetic principles as a whole. Resilience and adaptation capability play a major role in longevity, as we discussed above, and both these features are significantly influenced by the state of health of PNEI system. Any psychological, physical or biological stressor positively or negatively interferes with PNEI components and viceversa. Acute stressors at low doses and for a short duration seem to play a role in longevity medicine, generating a beneficial adaptation response which increases the tolerance level to further exposure to stressors at higher doses (a typical form of resilience) [71].

The most studied and proven stimuli which may induce a

Table 4

PNEI and Hormesis

Authors - year	Topics	Outcomes
Calabrese et al. [70]	Cellular stress responses, hormetic phytochemicals and vitagenes in aging and longevity	Dietary antioxidants, such as polyphenols and L-carnitine/acetyl-L-carnitine, have a neuroprotective role through the activation of hormetic pathways, including vitagenes, which encode for heat shock proteins (Hsp) , the thioredoxin and the sirtuin protein systems.
Calabrese et al. [71]	How does hormesis impact biology, toxicology, and medicine?	Hormesis refers to adaptive responses of biological systems to moderate environmental or self-imposed challenges through which the system improves its functionality and/or tolerance to more severe challenges.
Calabrese et al. [72]	Preconditioning is hormesis. Part I: Documentation, dose-response features and mechanistic foundations	Hormetic doses of a variety of agents stimulated adaptive responses that conditioned and protected cells against the subsequent toxicity resulting from a second, higher dose of the same or different agents.
Calabrese et al. [73]	Preconditioning is hormesis. Part II: How the conditioning dose mediates protection: Dose optimization within temporal and mechanistic frameworks	The biological/biomedical effects induced by conditioning represent a specific type of hormetic dose response and thereby contribute significantly to a generalization of the hormetic concept.
Calabrese et al. [74]	Pre- and Post-conditioning hormesis in elderly mice, rats, and humans; its loss and restoration	Common rearing practices (i.e., no exercise; ad libitum feeding) are strongly associated with the loss of preconditioning to prevent ischemic reperfusion damage to the heart in old/elderly rodents. Substantial restoration of preconditioning in old/elderly animal models is affected *via* various types of exercise protocols, dietary interventions and pharmacological means.
Hanisch [75]	Microglia as a source and target of cytokines	Dysregulation of microglial cytokine production could promote harmful actions of the defense mechanisms, result in direct neurotoxicity, as well as disturb neural cell functions
Chabot et al. [76]	Mechanisms of IL-10 Production in Human Microglia-T Cell Interaction	IL-10 generation is cell contact dependent between microglia T-cells and lymphocytes
Ziv et al. [77]	Immune-based regulation of adult neurogenesis; Brain Behavior and Immunity	Immune cells contribute to maintaining life-long hippocampal neurogenesis. Too little immune activity (as in immune deficiency syndromes) or too much (as in severe inflammatory diseases) can lead to impaired hippocampal-dependent cognitive abilities.
Thanos et al. [78]	Food Restriction Markedly Increases Dopamine D2 Receptor (D2R) in a Rat Model of Obesity as Assessed With *In vivo* IPET Imaging ([11C] Raclopride) and *In vitro* ([3 H] Spiperone)	Lack of a significant difference between food restricted animals (obese and lean) suggests that the differences in dopamine activity and D2 receptors levels between unrestricted obese and unrestricted lean rats are modulated by access to food.
Katz et al. [79]	Brain-Derived Neurotrophic Factor Is Critically Involved in Thermal-Experience-Dependent Developmental Plasticity	When BDNF in the hypothalamus was "knocked down" , thermal establishment was impaired, reaction to thermal challenge was altered, and the ability to maintain body temperature and body weight under harsh conditions was reduced.
Kyriazis et al. [81]	Nonlinear stimulation and hormesis in human aging: practical examples and action mechanisms	Any type of a hormetic dose-response phenomenon has an effect that does not depend on the type of stressor and that it can affect any biological model. Novel types of innovative, mild, repeated stress or stimulation that challenge a biological system in a dose-response manner are likely to have an effect to delay, prevent, or reverse age-related changes in humans.

hormetic response in living organisms are: fasting, limited cold/heat exposure, moderate exercising, resistance respiratory training, polyphenols ingestion, oxygen deprivation or hyper-exposure, radiations, spiritual/intellectual/social stimulation [71-74]. Table 4 summarizes a few studies and concepts regarding the hormesis pathways.

In the therapeutic field, the concept of inflammation cannot be separated from the one of hormesis; different levels and duration of inflammation may represent beneficial, or harmful stimuli for human health [74].

It has been shown that the three main proinflammatory cytokines (IL-1, IL-6, TNF-a) are normally produced at low doses from microglial cells and astrocytes in the brain (particularly in the hypothalamus, hippocampus, thalamus and basal ganglia), as part of the physiological processes of brain activation [75]. Even in the presence of T cells, microglial cells assume a "protective" profile, which stimulates neurogenesis, especially in the hippocampus. On the contrary, in case of inflammatory activation with high doses of cytokines, the microglial cells assume a distinguishable profile, also from the morphological point of view, and the blocking of neurogenesis occurs [76].

An experimental study has repeatedly documented in animals that an immune deficiency is related to a blockage of hippocampal neurogenesis [77]. In contrast, a stimulating environment or a non-stressful physical activity causes a moderate release of a few inflammatory mediators that however stimulate neurogenesis by increasing the concentration of brain-derived neurotrophic factor (BDNF), the most important neurotrophic substance targeting neuronal growth and synapses development. On the contrary an excessive inflammation can cause brain damage also as a consequence

of the blockage of new neurons formation.

The limbic system, which is composed of hypothalamus, amygdala and other neuronal structures, rules basic urges and desires together with temperature and sleep regulation, hence it is strictly involved in PNEI functionality. The possible primary hormetic stressors which interact with limbic system are represented by caloric restriction, fasting, cold/heat exposure and other forms of required adaptation; these hormetic stimuli can significantly impact hypothalamus and amygdala regulation.

In fact limbic system (N of PNEI) may respond less to conventional medicine, drugs, intentional behaviours, especially at long term; conversely hormetic pathways may influence limbic system more stably, for example with fasting through increase of dopamine receptors [78], or with high/low temperature exposure through BDNF increase [79].

Other forms of hormesis and PNEI interaction regard the possibility to have mental and social stimulation through environmental enrichment, social and spiritual activities, technology (i.e. internet) which are able to act in a hormetic fashion on the PNEI components: a possible positive stimulation has been emphasized by Kyriazis within this field [80].

Conclusion

Since the early seventies literature data have highlighted a relevant role for PNEI in the aging process [1,81] and in any degenerative disease; more recently a significant role has been attributed to PNEI system in psychiatric diseases as well [82]. chronic stress and psychological/social discomfort may result in pathophysiological clinical manifestations and interfere with the immune system and favour CLGCI and inflammaging. The latter process has a pivotal role in disparate pathologies, from autoimmune diseases, diabetes, atherosclerosis to neurodegeneration and cancer.

Literature data show that several measures aimed at improving PNEI function, such as stress management, nutrition, nutraceuticals (e.g. polyphenols, melatonin), may be beneficial in targeting CLGCI and subsequently aging processes. Hormetic stressors may represent a further potential mechanism to stimulate PNEI system, which may ultimately result in an improvement in terms of resilience and healthy aging.

Conflict of Interest

The authors declare that they have no conflict of interest with regard to the content of this article.

References

[1] Besedovsky HO, Rey AD. Physiology of psychoneuroimmunology: A personal view. Brain Behav Immun 2007;21:34-44.
[2] Ader R, Cohen N, Felten D. Psychoneuroimmunology: interactions between the nervous system and the immune system. Lancet 1995;345:99-103.
[3] Zeng Y, Shen K. Resilience Significantly Contributes to Exceptional Longevity. Curr Gerontol Geriat Res 2010:525693.
[4] What is health? The ability to adapt. Lancet 2009;373:781.
[5] Guidi LA, Tricerri AA, Frasca DB, *et al.* Psychoneuroimmunology and aging; Gerontol 1998;44:247-261.
[6] Vitetta L, Anton B, Cortizo F, *et al.* Mind-body medicine: stress and its impact on overall health and longevity; Ann N Y Acad Sci 2005;1057:492-505.
[7] Wirtz PH, von Känel R. Psychological stress, inflammation, and coronary heart disease. Curr Cardiol Rep 2017;19:111.
[8] Alcocer-Gómez E, Castejón-Vega B, Cordero MD. Stress-induced NLRP3 inflammasome in human diseases. Adv Protein Chem Struct Biol 2017;108:127-162.
[9] Bellinger DL, Millar BA, Perez S, *et al.* Sympathetic modulation of immunity: Relevance to disease. Cell Immunol 2008;252:27-56.
[10] BienenstocK J. Allergy and the nervous system. Chem Immunol Allergy 2012;98:I–XII.
[11] Rosa AC, Fantozzi R. The role of histamine in neurogenic inflammation. Br J Pharmacol 2013;170:38-45.
[12] Capron L. Inflammation and atherosclerosis. J des Mal Vasc 1989;1:3-12.
[13] Yu RH, Ho SC, Lam CW, *et al.* Psychological factors and subclinical atherosclerosis in postmenopausal chinese women in hong kong. Maturitas 2010;67:186-91.
[14] Fan LB, Li J, Wang XP, *et al.* Association between job stress and blood lipids among university staff in Yunnan province. Zhonghua Xin Xue Guan Bing Za Zhi 2009;37:454-7.
[15] Xu W, Hang J, Gao W, *et al.* Association between job stress and newly detected combined dyslipidemia among chinese workers: Findings from the SHISO study. J Occup Health 2011;53:334-42.
[16] Neves VJ1, Moura MJ, Almeida BS, *et al.* Chronic stress, but not hypercaloric diet, impairs vascular function in rats. Stress 2012;15:138-48.
[17] Dantzer R, O'Connor JC, Freund GG, *et al.* From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008;9:46-56.
[18] Dantzer R, O'Connor JC, Lawson MA, *et al.* Inflammation-associated depression: from serotonin to kynurenine. Psychoneuroendocrinol 2011;36:426-36.
[19] Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999;99:2192-217.
[20] Rozanski A, Blumenthal JA, Davidson KW, *et al.* The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. J Am Coll Cardiol 2005;45:637-51.
[21] Yusuf S, Hawken S, Ounpuu S, *et al.* Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. Lancet 2004;364:937-52.
[22] Halaris A. Inflammation, heart disease, and depression. Curr Psychiatry Rep 2013;15:400.
[23] Chida Y, Hamer M, Wardle J, *et al.* Do stress-related psychosocial factors contribute to cancer incidence and survival?. Nat Clin Pract Oncol 2008;5:466-75.
[24] Franceschi C, Valensin S, Bonafè M, *et al.* The network and the remodeling theories of aging: historical background and new perspectives. Exp Gerontol 2000;35:879-96.
[25] Fougère B, Boulanger E, Nourhashémi F, *et al.* Chronic inflammation: accelerator of biological aging. J Gerontol A Biol Sci Med Sci 2017;72:1218-25.
[26] Appleton AA, Buka SL, Loucks EB, *et al.* A prospective study of positive early-life psychosocial factors and favorable cardiovascular risk in adulthood. Circulation 2013;127:905-12.
[27] Han K, Lee Y, Gu J, *et al.* Psychosocial factors for influencing healthy aging in adults in korea. Health Qual Life Outcomes 2015;13:31.
[28] Levy BR, Slade MD, Kunkel SR, *et al.* Longevity increased by positive self-perceptions of aging. J Pers Soc Psychol 2002;83:261-70.
[29] Sadler ME, Miller CJ, Christensen K, *et al.* Subjective wellbeing and longevity: a co-twin control study. Twin Res Hum Genet 2011;14:249-56.
[30] Vaillant G. Triumphs of experience: the men of the harvard grant study (1st edition). Harvard University Press 2012.
[31] Epel E, Daubenmier J, Moskowitz JT, *et al.* Can meditation slow rate of cellular aging? Cognitive stress, mindfulness, and telomeres. Ann N Y Acad Sci 2009;1172:34-53.
[32] Epel ES, Blackburn EH, Lin J, *et al.* Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci USA 2004;101:17312-5.
[33] Entringer S, Epel ES, Kumsta R, *et al.* Stress exposure in intrauterine life is associated with shorter telomere length in young adulthood. PNAS 2011;108:E513-8.
[34] Entringer S, Epel ES, Lin J, *et al.* Maternal psychosocial stress during pregnancy is associated with newborn leukocyte telomere length. Am J Obstet Gynecol 2013;208:134.e1-7.

[35] Kroenke CH, Epel E, Adler N, *et al.* Autonomic and adrenocortical reactivity and buccal cell telomere length in kindergarten children. Psychosom Med 2011;73:533-40.
[36] Ng F, Berk M, Dean O, *et al.* Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. Int J Neuropsychopharmacol 2008;11:851–876
[37] De la Fuente M. Role of neuroimmunomodulation in aging. Neuroimmunomodulation 2008;15:213-223.
[38] Vida C, Gonzalez E, De la Fuente M. Increase of oxidation and inflammation in nervous and immune systems with aging and anxiety. Curr Pharm Des 2014;29:4656-4678.
[39] Van Diest I, Verstappen K, Aubert AE, *et al.* Inhalation/exhalation ratio modulates the effect of slow breathing on heart rate variability and relaxation. Appl Psychophysiol Biofeedback 2014;39:171-80.
[40] Lin IM, Tai LY, Fan SY. Breathing at a rate of 5.5 breaths per minute with equal inhalation-to-exhalation ratio increases heart rate variability. Int J Psychophysiol 2014;91:206-11.
[41] Brown RP, Gerbarg LP, Muench F. Breathing practices for treatment of psychiatric and stress-related medical conditions. Psychiatr Clin N Am 2013;36:121-140.
[42] Tolahunase M, Sagar R, Dada R. Impact of yoga and meditation on cellular aging in apparently healthy individuals: a prospective. Open-label single-arm exploratory study. Oxid Med Cell Longev 2017;7928981.
[43] Freitas TH, Hyphantis TN, Andreoulakis E, *et al.* Religious coping and its influence on psychological distress, medication adherence, and quality of life in inflammatory bowel disease. Rev Bras Psiquiatr 2015;37:219-27.
[44] Li S, Stampfer MJ, Williams DR, VanderWeele TJ. Association of religious service attendance with mortality among women. JAMA Intern Med 2016;176:777-85.
[45] Chellew K, Evans P, Fornes-Vives J, *et al.* The effect of progressive muscle relaxation on daily cortisol secretion. Stress 2015;18:538-44.
[46] Ferreira JB, Plentz RD, Stein C, *et al.* Inspiratory muscle training reduces blood pressure and sympathetic activity in hypertensive patients: A randomized controlled trial. Int J Cardiol 2013;166:61-7.
[47] Pęciłło M. The concept of resilience in OSH management: a review of approaches. Int J Occup Saf Ergon 2016;22:291-300.
[48] Jeste DV, Savla GN, Thompson WK, *et al.* Association between older age and more successful aging: critical role of resilience and depression. Am J Psychiatry 2013;170:188-96.
[49] Quintana DS, Kemp AH. The relationship between mental and physical health: Insights from the study of heart rate variability. Int J Psychophysiol 2013;89:288-96.
[50] Appelhans BM, Luecken LJ. Heart rate variability as an index of regulated emotional responding. Rev Gen Psychol 2006;10:229-40.
[51] Tracy KJ. The inflammatory reflex. Nature 2002;420:853-9.
[52] Guarini S, Altavilla D, Cainazzo MM, *et al.* Efferent vagal fibre stimulation blunts NFkB activation and protects against hypovolemic hemorrhagic shock. Circulation 2003;107:1189-94.
[53] Huston JM, Ochani M, Rosas-Ballina M, *et al.* Splenectomy inactivates the cholinergic antiinflammatory pathway during lethal endotoxemia and polymicrobial sepsis. J Exp Med 2006;203:1623-8.
[54] Nance DM. Autonomic innervation and regulation of the immune system (1987-2007). Brain Behav Immunity 2007;21:736-45.
[55] Xu Y, Zhao W, Li T, *et al.* Effects of acupuncture for the treatment of endometriosis-related pain: a systematic review and meta-analysis. PLoS One 2017;12:e0186616.
[56] Gomez-Pinilla F, Nguyen TT. Natural mood foods: the actions of polyphenols against psychiatric and cognitive disorders. Nutr Neurosci 2012;15:127-33.
[57] Willcox DC, Scapagnini G, Willcox BJ. Healthy aging diets other than the mediterranean: a focus on the okinawan diet. Mech Ageing Dev 2014;136-137:148-62.
[58] Matsuoka Y, Nishi D. The possibility of omega-3 fatty acid improving resilience. Jap J Gen Hosp Psychiat 2012;24:25-32.
[59] Kiecolt-Glaser JK. Stress, food, and inflammation: psychoneuroimmunology and nutrition at the cutting edge. Psychosom Med 2010;72:365-9.
[60] El Aidy S. Dinan TG, Cryan JF. Gut microbiota: the conductor in the orchestra of immune-neuroendocrine communication. Clin Therapeutics 2015;37:954-67.
[61] Sadowska-Bartosz I, Bartosz G. Effect of antioxidants supplementation on aging and longevity. BioMed Res Int 2014:404680.
[62] Si H, Liu D. Dietary antiaging phytochemicals and mechanisms associated with prolonged survival. J Nutr Biochem 2014;25:581-91.
[63] Rattan SI. Rationale and methods of discovering hormetins as drugs for healthy ageing. Expert Opin Drug Discov 2012;7:439-48.
[64] Tizabi Y, Hurley LL, Qualls Z, *et al.* Relevance of the anti-inflammatory properties of curcumin in neurodegenerative diseases and depression. Molecules 2014;19:20864-79.
[65] Bourre JM. Dietary omega-3 fatty acids and psychiatry: mood, behaviour, stress, depression, dementia and aging. J Nutr Health Aging 2005;9:31-8.
[66] Srinivasan V, Smits M, Spence W, *et al.* Melatonin in mood disorders. World J Biol Psychiatry 2006;7:138-51.
[67] Lieberman HR, Waldhauser F, Garfield G, *et al.* Effects of melatonin on human mood and performance. Brain Res 1984;323:201-7.
[68] Lanfumey L, Mongeau R, Hamon M. Biological rhythms and melatonin in mood disorders and their treatments. Pharmacol Ther 2013;138:176-84.
[69] Lissoni P, Messina G, Tantarelli R, *et al.* The psychoneuroimmunotherapy of human immune-mediated systemic diseases, including cancer and autoimmune diseases. J Mol Oncol Res 2017;1:7-13.
[70] Calabrese V, Cornelius C, Dinkova-Kostova AT, *et al.* Cellular stress responses, hormetic phytochemicals and vitagenes in aging and longevity. Biochim Biophys Acta 2012;1822:753-83.
[71] Calabrese EJ, Mattson MP. How does hormesis impact biology, toxicology, and medicine?. Aging Mechan Dis 2017;3:13.
[72] Calabrese EJ. Preconditioning is hormesis. Part I: Documentation, dose-response features and mechanistic foundations. Pharm Res 2016;110:242-64.
[73] Calabrese EJ. Preconditioning is hormesis. Part II: How the conditioning dose mediates protection: Dose optimization within temporal and mechanistic frameworks. Pharm Res 2016;110:265-75.
[74] Calabrese EJ. Pre- and Post-conditioning hormesis in elderly mice, rats, and humans; its loss and restoration. Biogerontol 2016;17:681-702.
[75] Hanisch UK. Microglia as a source and target of cytokines. Glia 2002;40:140-55.
[76] Chabot S, Williams G, Hamilton M, *et al.* Mechanisms of IL-10 production in human microglia-t cell interaction. J Immunol 1999;162:6819-28.
[77] Ziv Y, Schwartz M. Immune-based regulation of adult neurogenesis. Brain Behav Immunity 2008;22:167-76.
[78] Thanos PK, Michaelides M, Piyis YP, *et al.* Food restriction markedly increases dopamine D2 receptor (D2R) in a rat model of obesity as assessed with in-vivo lPET imaging ([11C] raclopride) and in-vitro ([3 H] spiperone). Autoradiography Synapse 2008;62:50-61.
[79] Katz A, Meiri N. Brain-derived neurotrophic factor is critically involved in thermal-experience-dependent developmental plasticity. J Neurosc 2006;26:3899-907.
[80] Kyriazis M. Nonlinear stimulation and hormesis in human aging: practical examples and action mechanisms. Rejuvenation Res 2010;13:445-52.
[81] Scapagnini U. Psychoneuroendocrinoimmunology: the basis for a novel therapeutic approach in aging. Psychoneuroendocrinol 1992;17:411-420.
[82] Bottaccioli AG, Bottaccioli F, Minelli A. Stress and the psyche-brain-immune network in psychiatric diseases based on psychoneuroendocrineimmunology: a concise review. Ann N Y Ac Sci 2018.