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Author	Family Name	**Calabrese**
	Particle	
	Given Name	**Vittorio**
	Prefix	
	Suffix	
	Role	
	Division	Department of Biomedical and Biotechnological Sciences, School of Medicine
	Organization	University of Catania
	Address	Via Santa Sofia, 97-95125, Catania, Italy
	Email	calabres@unict.it
Author	Family Name	**Scuto**
	Particle	
	Given Name	**Maria**
	Prefix	
	Suffix	
	Role	
	Division	Department of Biomedical and Biotechnological Sciences, School of Medicine
	Organization	University of Catania
	Address	Via Santa Sofia, 97-95125, Catania, Italy
	Email	Mary-amir@hotmail.it
Corresponding Author	Family Name	**Calabrese**
	Particle	
	Given Name	**Edward**
	Prefix	
	Suffix	
	Role	
	Division	Department of Environmental Health Sciences
	Organization	University of Massachusetts
	Address	Morrill I, Amherst, MA, N34401003, USA
	Email	edwardc@schoolph.umass.edu

Abstract	The concept of acquired resilience and its role in medicine and public health has emerged as a central topic for the new decade. Stress is a response to any environmental adversity (i.e., biological, emotional and cognitive) but dysregulation of adaptive stress responses which lowers resilience and health, can increase vulnerability to pathological conditions such as brain disorders, particularly, neuropsychiatric (i.e.,

schizophrenia, depression, anxiety, autism spectrum disorders), and neurodegenerative diseases (i.e., Alzheimer's diseases and Parkinson's disease). Mild stress can be beneficial by upregulating adaptive responses which enhance biological performance and protect against subsequent toxic challenges. In contrast, toxic stress reflecting an inability to cope, results in a dysregulation of adaptive stress response mechanisms and low resilience which can increase vulnerability to illness. In this context, resilience is the process of adapting and successfully coping with adverse life events, including chronic stress, socio-environmental factors, trauma, some type of catastrophe, physical or sexual abuse, negligence or parental mental illness. Detailed evaluations of biological systems showing acquired resilience reveal an hormetic biphasic dose response relationship, being reported as the result of either a direct low dose stimulation or within the context of a preconditioning experimental protocol. The hormetic dose response defines the expression, amplitude, duration and limitations of the acquired resilience in all biological systems. These acquired resilience-hormetic dose responses are reported in the pharmacology and nutritional literature with considerable information now clarifying underlying mechanisms at the level of receptor and cell signaling pathways. The study of human resilience is still a mostly phenomenological literature which has only begun to characterize biological factors in resilient individuals that are associated with more successful coping responses. Integration, optimization and tailoring of such developments to the treatment of patients offers a profound challenge and opportunities to the progress of biomedical sciences and therapeutic medicine.

Keywords Resilience - Healthy brain - Hormesis - Vitagenes - Plant polyphenols

Chapter 28
Hormesis, Resilience and Mental Health: Enhancing Public Health and Therapeutic Options

Vittorio Calabrese, Maria Scuto, and Edward Calabrese

Abstract The concept of acquired resilience and its role in medicine and public health has emerged as a central topic for the new decade. Stress is a response to any environmental adversity (i.e., biological, emotional and cognitive) but dysregulation of adaptive stress responses which lowers resilience and health, can increase vulnerability to pathological conditions such as brain disorders, particularly, neuropsychiatric (i.e., schizophrenia, depression, anxiety, autism spectrum disorders), and neurodegenerative diseases (i.e., Alzheimer's diseases and Parkinson's disease). Mild stress can be beneficial by upregulating adaptive responses which enhance biological performance and protect against subsequent toxic challenges. In contrast, toxic stress reflecting an inability to cope, results in a dysregulation of adaptive stress response mechanisms and low resilience which can increase vulnerability to illness. In this context, resilience is the process of adapting and successfully coping with adverse life events, including chronic stress, socio-environmental factors, trauma, some type of catastrophe, physical or sexual abuse, negligence or parental mental illness. Detailed evaluations of biological systems showing acquired resilience reveal an hormetic biphasic dose response relationship, being reported as the result of either a direct low dose stimulation or within the context of a preconditioning experimental protocol. The hormetic dose response defines the expression, amplitude, duration and limitations of the acquired resilience in all biological systems. These acquired resilience-hormetic dose responses are reported in the pharmacology and nutritional literature with considerable information now clarifying underlying mechanisms at the level of receptor and cell signaling pathways. The study of human resilience is still a mostly phenomenological literature which has only begun to characterize

V. Calabrese · M. Scuto
Department of Biomedical and Biotechnological Sciences, School of Medicine, University of Catania, Via Santa Sofia, 97-95125 Catania, Italy
e-mail: calabres@unict.it

M. Scuto
e-mail: Mary-amir@hotmail.it

E. Calabrese (✉)
Department of Environmental Health Sciences, University of Massachusetts, Morrill I, Amherst, MA N34401003, USA
e-mail: edwardc@schoolph.umass.edu

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28.1 Introduction

Resilience, as the ability to adequately adapt and respond to homeostatic perturbations, is a recent emerging concept. Although resilience has been associated with positive health effects, the neurobiological basis of resilience is still a matter of investigation and remains an open question.

It is generally recognized now that multiple factors, such as severity and number of traumatic events during prenatal neurodevelopment and adolescence, timing of exposure to adversity, developmental history, cognitive flexibility and environmental changes such as toxicant exposure compromise health and wellbeing over the lifespan. Consistent with this notion, in the attempt to operationalize at cellular level the neurobiology of stress resistance, cellular resilience describes the ability of a cell to cope with detrimental metabolic and signaling conditions where cellular metabolism does not collapse immediately after the hit or enter into cell death. Rather, this cellular ability puts in motion a programmed cell life program through stress responsive signaling which promotes a new homeostasis under stress. The processes of reverting "back to normal" have not been studied so extensively at the cellular level. The defense and resilience programs include a number of cellular stress responses, such as rearrangements in energy metabolism, oxidative stress responses, including hypoxia signaling via HIF-1, the heat shock response via HSF-1, the antioxidant response via Nrf-2, stress kinase signaling via JNK and AP-1, DNA damage responses via p21 or BCL2, and the unfolded protein response/amino acid starvation response via ATF-4/ATF-6 activation of anti-apoptotic pathways and DNA repair mechanisms. The actual contribution of these adaptive responses to reestablishing homeostasis represents an emerging area of interest in need of clarification. Efficient functioning of resilience processes, by enhancing endogenous cellular redox homeostatic mechanisms, integrate adaptive stress responses via the heat shock and Nrf2 related pathways (Fig. 28.1), as well as sirtuins via AKT/mTOR signaling, thus representing a complex operational network under control of genes, termed vitagenes (Calabrese et al. 2010) (Fig. 28.2), as well as epigenetic changes that leave a molecular "memory/scar"—mirroring alterations that are the consequence of the stress experienced by the cell.

These memories might have long-term consequences, both positive (resistance) and negative (vulnerability), that contribute to chronic and delayed manifestations of hazard and, ultimately, disease. Compromised adaptive responses to adversity, such as brain trauma or psychological stresses, i.e., low resilience, can increase vulnerability to pathological conditions such as anxiety, depression, post-traumatic stress

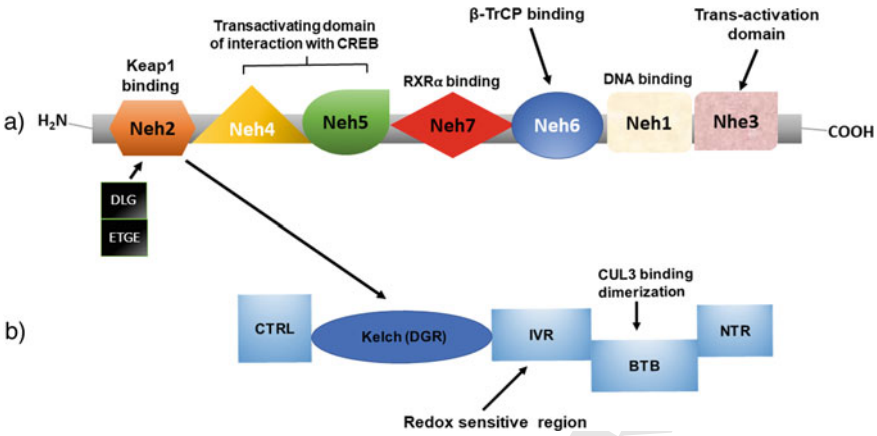

Fig. 28.1 Schematic representation illustrating domains structure of Nrf2-keap1. **a** Nrf2 contains seven highly conserved homologous domains (Neh 1–7). Neh1 is a DNA binding protein associated to sMaf in form of heterodimers which mediates binding to ARE in the promoter region of Nrf2. Neh2 is keap1 binding protein domain, containing the low affinity DLG motif and high affinity ETGE motif responsible of ubiquitination and proteosomal degradation of Nrf2. Neh3 is the transactivation domain recruiting CHD6. Neh4 and Neh5 are transactivation domains that recruit CREB. The Neh6 and Neh7 domains mediate interaction with β-TrCP and, respectively, RXRα, both negative regulators of Nrf2. Keap1 is divided into five regions: CTR region; BTB region which binds Cul3 ligase responsible of keap1 dimerization; **b** Kelch (DGR) region consisting of six repeated sequences that interact with DLG and ETGE of Nrf2, IVR redox sensitive region containing cysteine residues associated to Nrf2 ubiquitination. NTR region. Nuclear factor-erythroid 2 p45-related factor 2 (Nrf2), Kelch-like ECH-associated protein 1 (keap 1), cAMP response element-binding protein (CREB), retinoid X receptor alpha (RXRα), β-transducin repeat-containing protein (β-TrCP), small musculoaponeurotic fibrosarcoma proteins (sMaf), antioxidant response element (ARE), chromo-ATPase/helicase DNA-binding protein 6 (CHD6)

disorders (PTSD) (Sexton et al. 2015), and neurodegenerative pathologies (Gupta et al. 2014), although not everyone exposed to adversity develops these disorders. Higher-resilient individuals, on the other hand, show an enhanced ability to bounce back from adverse events, revealing greater emotional and cognitive control and are more persistent. Linked to the areas of disaster research, the concept of resilience, applied initially to critical infrastructures, has been consolidated in the process of prevention for subsequent possible hits (Taleb 2007). In the brain, the corresponding neurobiological Achilles' heel is represented by mitochondria, where reduced efficiency of the electron transport chain (ETC), enhancing oxidative stress by ROS and reducing energy production occurring in response to many hazards, initiates apoptotic cytochrome C release associated to mitochondrial dysfunction and neurodegeneration. Consistent with this notion, in facing challenges, adaptive responses (hormetic triggers) such as caloric restriction or increased metabolic demand would generate an improved mitochondrial function efficiency, which substantially contributes to the maintenance of homeostasis (Nunn et al. 2016). Hence, the brain is continuously

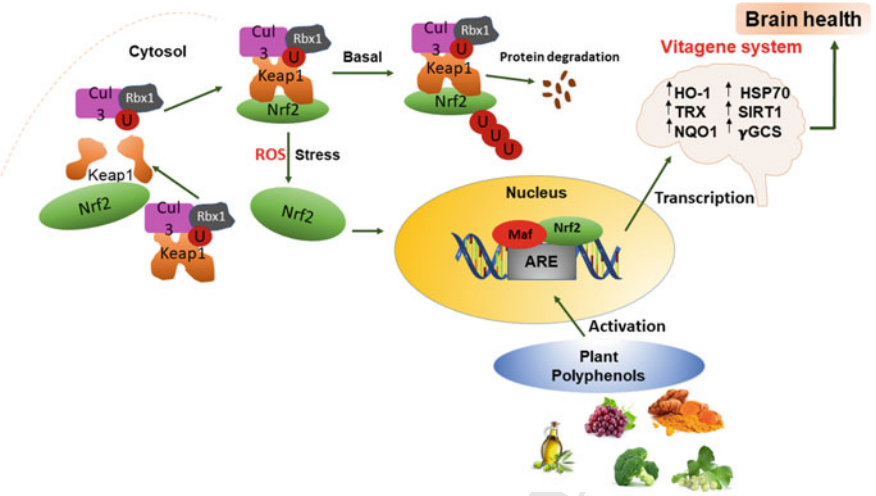

Fig. 28.2 Modulation of Nrf2-vitagene pathway by plant polyphenols in the brain. In basal conditions Nrf2 is bound to its inibitor Keap1 and is restricted to the cytosol, where it undergoes ubiquitination and proteasomal degradation via association with the Cul3-Rbx1 based E3/ubiquitin ligase complex. Under stress conditions, Nrf2 is released from Keap1 and is translocated into the nucleus where it binds to the phase 2 of ARE in etreorodimeric combination with Maf transcription factor in the DNA promoter region. Plant polyphenols are small molecules that reverse stress and ROS production by activating Nrf2 nuclear translocation and transcription of neuroprotective vitagenes. The upregulation of vitagene pathway such as HO-1, Hsp70, Trx, sirtuin Sirt1, NQO1, γ-GCS improves brain health and protect against neurodegenerative damage. Nuclear factor-erythroid 2 p45-related factor 2 (Nrf2), Kelch-like ECH-associated protein 1 (Keap1), antioxidant response element (ARE), heme-oxygenase 1 (HO-1), heat shock protein 70 (Hsp70), thioredoxin (Trx), sirtuin 1 (Sirt1), NAD(P)H: quinone oxidoreductase 1 (NQO1), γ-glutamylcysteine synthetase (γ-GCS)

adapting to perturbations in bodily homeostasis, and a resilient brain integrates adaptive responses that regulate behaviors associated with coping, fear, attention, cognitive flexibility, and emotional regulation (Baratta et al. 2013; Russo et al. 2012). More generally, high resilient individuals display more effective modulation of brain circuits involved in emotion and fear (Southwick et al. 2014).

A recent paradigm shift in operationalizing resilience has moved away from the focus on the non-emergence of pathology or symptoms after exposure to adversity, to include "resilient-conductive" factors such as personality traits, confidence, flexibility, optimism, or emotional liability, which can help promote positive subjective appraisal, negotiation, adaptation, or management of adverse situations with increased coping (Kalisch et al. 2015). Yet, information on the neurobiological correlates of these complex psychosocial and spiritual factors is lacking (Pietrzak et al. 2010). Individual traits such as subjective well-being (both hedonic or eudaimonic) could also be protective factors against adversity (Di Fabio et al. 2015). Hedonic well-being refers to cognitive evaluation of life satisfaction and positive affect, whereas eudaimonic well-being is related to the determination of life-meaning and self-actualization. Resilience is related to both types of well-being (Di Fabio et al.

2015). Positive affect is thought to facilitate resilience by broadening one's attention and coping abilities, and by decreasing susceptibility to disease through increased vagal control (Oveis et al. 2009). The overlap between measures of positive affect and resilience has also been observed in various conditions such as chronic pain (Strand et al. 2006) or brain trauma. The identification of neurobiological correlates associated with resilience endophenotype may therefore be a critical first step in the identification of individuals with increased vulnerability to develop diseases. Identifying brain signatures of resilience as biomarkers of vulnerability to stress-related diseases can have implications for the development of training interventions, such as preconditioning or post conditioning effects associated to hormesis, which increase effective coping and management of stress conditions.

In the brain, a resilient neuronal cell does not necessarily correspond to a healthy cell, as in the case of a cancerous phenotype being very resilient towards chemotherapy. In some tumor cells, high resilience mechanisms lead to a resistance to drugs despite being exposed to the same concentrations as their neighboring cells. Such changes can be long-term, or even permanent, constituting cellular biological memories associated with beneficial outcomes, as in the context of cellular hormesis. Such beneficial outcomes, particularly with respect to ischemia–reperfusion, can be seen where an initial stressor makes cells more resilient to subsequent stress to organs. Here, the so called "pre-conditioning", or alternatively after an adverse situation, a subsequent stressor "post-conditioning", are used and developed, both experimentally and clinically (Smirnova et al. 2015). Long-term effects can however also be detrimental and lead to adverse outcomes, especially when exposure is of limited duration, as in the case of mixture toxicities.

The underlying strategy of hormesis in these cases entails the upregulation of adaptive mechanisms that results in the development of biological resilience. New resilient phenotypes will conform to the quantitative and temporal features of the hormetic dose-time response relationship, often within a preconditioning context. While the amplitude of induced resilience is modest, being about 30–60% greater than the control group/background at maximum, and the duration of resilience is limited, it appears possible to significantly extend the duration of the resilience in some models depending on preconditioning stimulation methods (Gidday 2015). Similar insights on increasing the amplitude of the resilient phenotype remain to be explored. Since Parkinson's Disease (PD) onset and progression is highly age dependent, it is important to recognize that preconditioning-induced hormetic resilience decreases profoundly with age in a variety of animal models. However, some success has been achieved in restoring pathway functions via various exercise schemes, dietary modifications and pharmacological approaches (Calabrese et al. 2015, 2016, 2018b).

Ultimately, the concept of resilience is difficult to operationalize, since it encapsulates many divergent behavioral phenotypes. Indeed, the study of human resilience is still a mostly phenomenological literature which has only begun to characterize biological factors in resilient individuals that are associated with more successful coping responses. Thus, integration, optimization and tailoring of such developments to the treatment of patients offers a profound challenge and opportunities to the progress of biomedical sciences and therapeutic medicine. In the subsequent

sections, we aim to provide evidence for possible prevention and early intervention approaches targeting humans and animals, and their correlation with environmental stressors, that can reduce the risk of brain disorders (i.e., neurodegenerative and neuropsychiatric disorders) and foster resilience mechanisms which maintain cellular homeostasis in response to stressors or adverse life experiences.

28.2 Resilience and Brain Health in Early Life

A growing field of recent research is focusing on the concept of resilience in the context of early brain health and its role in successful aging in order to elucidate neuroprotective resilient pathways and activation of stress responses against stress-related neuropsychiatric and neurodegenerative disorders. In this context, resilience is an active brain process that involves adaptive synaptic plasticity and cellular coping mechanisms to face the negative effects of stressful early experiences (i.e., physical and sexual abuse, socio-emotional neglect and maltreatments) (Russo et al. 2012; Southwick et al. 2014). In contrast, low resilience and high vulnerability to stressful or traumatic experiences, in particular during the prenatal neurodevelopment period and adolescence, alter brain circuits to affect sensory systems, network architecture and neuronal mediators involved in threat detection, emotional regulation and reward anticipation. These alterations leave a molecular mark on the genome in the form of epigenetic modifications that result in a "biological embedding" of these stressful life events throughout the life course, contributing to the development of mental illness such as psychiatric (i.e., depression, anxiety and post-traumatic stress disorder (PTSD)) and neurodegenerative disorders (i.e., Alzheimer's diseases) both in humans and animal models (Gravitz 2018; Teicher et al. 2016; Lesuis et al. 2018; Cohen et al. 2013). Moreover, preclinical studies reported that early life interventions modulate aversive memory reconsolidation in the dorsal hippocampus and may program the resilience or vulnerability to psychopathologies of traumatic memories later in life in rodents (Couto-Pereira et al. 2019). On the other hand, the identification of pro-resilience predictive pathways that confer neuroprotection by restoring cellular homeostasis following genetic, epigenetic and environmental stressors has been associated with positive mental outcomes such as reduced depression and mortality risk (Gooding et al. 2012) thus promoting lifespan and well-being (Jeste et al. 2013).

Psychological resilience is the ability to bounce back after a stressful or traumatic event (Southwick et al. 2012) and accounts for whether or not an individual develops a mental illness such as psychiatric and post-traumatic stress disorders (Cathomas et al. 2019). The epigenome may drive adaptive response mechanisms to environmental stressors or traumatic events, on the interface between dynamic environmental changes and the inherited genome, possibly allowing an "epigenotoxic effect" (Szyf 2007). Epigenetic modifications such as DNA methylation, DNA hydroxymethylation, histone modification, miRNA expression have been widely described to mediate the effect of these stressful experiences and to be involved in the vulnerability to depression (Januar et al. 2015), as well as for other stress-related brain disorders

(Nestler et al. 2016). Within this context, epigenetic alterations especially during early life sensory period provide a "*molecular memory*" to neuroplastic responses of environmental stressors and are central to the generation of vulnerable or resilient endophenotypes throughout life (Franklin et al. 2012; Silberman et al. 2016). The imprint from earlier exposures to adverse events, which can manifest as an epigenetic scar (rendering cells more sensitive) or resilience (more tolerant), needs to be considered to understand real-life exposures and measure risk. Sometimes the results of stressors are "bad memories," such as mutations, or other functional impairments that may predispose to disease or lead to adverse lifetime, or even transgenerational, outcomes. The fine line between resilience and maladaptation may need to be defined according to the situation. In the context of transgenerational transmission of early stress and mental disorder (i.e., schizophrenia, bipolar disorder and severe depression), a longitudinal cohort study reported early preventive strategies for transmission of risk or resilience from a parent with severe mental illness to their infant: stress-sensitivity, caregiving representation and quality of parent-infant interaction leading to the possibility of decreasing rate of mental illness in offspring (Harder et al. 2015).

Interestingly, a recent study suggested that early maternal care can epigenetically reprogram the behavior of offspring for their entire lifetime through modulation of neuroplasticity, neurogenesis, cell survival, resilience and specific stress response genes later in life (Vogel Ciernia et al. 2018). On the other hand, many studies reported that early maternal deprivation leads to epigenetic changes (i.e., histone acetylation and DNA methylation) in specific imprinted genes causing attention-deficit/hyperactivity disorder (ADHD), such as anxiolytic-behavior, hyperactivity as well as learning and memory deficits in adolescent rats and in maltreated children (Naumova et al. 2019).

Compelling evidence supports the crucial contribution provided by epigenetic memory in the form of changes to the DNA methylation pattern that could protect (offer resilience) or contribute to pathogenesis and cellular vulnerability to long-term subsequent stressors (Tyagi et al. 2015). Moreover, a recent study suggested that short- and long-term neonatal exposure to early life adversity induces epigenetic changes in dopaminergic molecular pathways and thus can alleviate or aggravate depressive-like symptoms in animal models of chronic stress later in life (Köhler et al. 2019).

All this highlights the importance of resilience and epigenetic processes to counteract vulnerable traits in humans and animal models of mental disorders. Hence, the epigenome may contribute to rendering the system more resistant to the development of neurodegenerative and psychiatric diseases occurring at a later stage of life.

28.2.1 Neurobiology of Brain Resilience

Recently, a large amount of evidence sheds light on the neurobiological factors underlying stress resilience, with particular emphasis on the hypothalamic–pituitary–adrenal (HPA) axis, brain-derived neurotrophic factor (BDNF), serotoninergic (5-HT), glutamatergic and γ-aminobutyric acid (GABA) systems (Faye et al. 2018). Modulating these receptors may promote resilience or vulnerability during stressful events.

28.2.1.1 Hypothalamic-Pituitary Axis

A neurobiological factor required for adaptive stress regulation is the hypothalamic-pituitary axis (HPA axis). The HPA axis is the central neuroendocrine pathway involved in response to stress and adaptation in humans and in animal models (Bomholt et al. 2004). The system is subject to diurnal circadian fluctuations and is also sensitive to both acute and chronic stress. Therefore, the HPA axis is important for understanding resilience or vulnerability to stress. Thus, individuals perceive stressful events differently, and when the stress response becomes overactive, the recovery mechanisms fail to work, leading to increased susceptibility to stress. Some individuals are less vulnerable to stress than others and are deemed resilient. When faced with adversity, people with low resilience are at risk of mental illnesses. Conversely, people who are able to integrate well socially, mentally or physically despite exposure to stress or adversity demonstrate resilience. It is important to note that childhood stress and trauma alter the HPA axis and its long-term dysregulation is associated with increased risk of adverse health outcomes. In addition, recent findings indicate that a dysregulation of the HPA axis induced by chronic stress in aged subjects correlates with negative health outcomes, such as a higher risk for mood disorders (i.e., anxiety and depression) and cognitive disorders (i.e., Alzheimer's disease), where individuals are predisposed to the effects of unstable emotional regulation (Kuhlman et al. 2018; Janak et al. 2015; Bao et al. 2018; Gupta et al. 2014).

In response to challenge or threat, the HPA axis produces a cascade of hormones leading to the release of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), which are neuropeptides from the hypothalamus and the pituitary, respectively. Lastly, this pathway culminates in the secretion of glucocorticoids and release of cortisol (or corticosterone in rodents) from the adrenal cortex. Diurnal cortisol is a physiological biomarker of HPA axis activity that contributes to stress resilience. Accordingly, altered diurnal or stress-induced secretion of the hormone cortisol (i.e., higher diurnal cortisol levels), combined with lower resilience resources (i.e., emotion dysregulation and poor social support), could predispose older adults to negative health outcomes (Gaffey et al. 2016). Thus, circulating cortisol levels change due to both environmental and endogenous influences. Several lines of evidence reveled that, in older adults, blunted diurnal cortisol secretion has

been associated with frailty (Johar et al. 2014), whereas lower diurnal cortisol is correlated with longevity (Noordam et al. 2010).

28.2.1.2 BDNF Pathway

It is well documented that stress is a common risk factor for a great range of brain disorders by targeting brain-derived neurotrophic factor (BDNF). BDNF is a potent neurotrophic factor implicated in synaptic plasticity, neurogenesis, memory processes and neuronal stress resistance (Marosi et al. 2014). Downregulation of BDNF expression has been associated with neuronal atrophy and death occurring in neurological disorders (Murer et al. 2001), and chronic stress typically decreases BDNF hippocampal expression (Smith et al. 1996). Reduced levels of BDNF have been reported not only under normal aging conditions but also in neuropathological conditions such as Alzheimer's disease (AD). Yet, experimental findings provide evidence on how the BDNF-TrkB pathway involved in neuroplasticity modulates stress vulnerability and resilience. Reduced BDNF-TrkB signaling contributes to vulnerability of β amyloid-related effects on cognition in the pathogenesis of AD (Devi et al. 2015).

28.2.1.3 Serotonin Pathway

Serotonin or 5-hydroxytryptamine (5-HT) is an important monoamine neurotransmitter implicated in stress resilience and vulnerability. 5-HT is synthetized in the body from the essential amino acid tryptophan (TRP) by the enzyme tryptophan hydroxylase (TRH). This neurotransmitter contributes to brain development and to the maintenance of normal brain function (Nordquist et al. 2010). Thus, low TRP leads to low 5-HT levels in the brain or exposure to psychosocial stress, which promotes the etiology of mood disorders in humans and animals (Gutknecht et al. 2015; Caspi et al. 2003). On the other hand, elevated levels of 5-HT are associated to neurotoxicity (Dell'Osso et al. 2016). Moreover, the 5-HT transporter gene is another actor of neurotransmission homeostasis and plays a role in modulating an individual's vulnerability or resilience to stress (Lesch et al. 1996). Stress induce alterations in the serotonin system are associated with structural and functional epigenetic changes in the brain. In this regard, epigenetic modifications such as hypermethylation in *HTR2A, HTR3A* and *5HHT* serotoninergic genes are associated with childhood trauma and psychiatric disorders in adulthood (Schechter et al. 2017; Kang et al. 2013). Serotonin 5-HT_{1A} receptors have been proposed as key mediators of serotonergic signaling in the hippocampus (Savitz et al. 2009). Chronic stress reduced the levels of 5-HT_{1A} receptors in different brain areas and increased the risk of depression in vulnerable patients and animals (Watanabe et al. 1993). On the other hand, high levels of hippocampal 5-HT_{1A} receptors represent a molecular marker that exerts resilience actions on limbic functioning and serotonergic homeostasis in the face of stress (Zurawek et al. 2019).

28.2.1.4 Glutamate Pathway

Glutamate is the main excitatory neurotransmitter in the central nervous system (CNS), and under physiological conditions, plays an important role in synaptic plasticity, learning, memory and emotional responses (Lin et al. 2019). Accumulating evidence suggests that less resilience is associated with dysregulation in glutamatergic neurotransmission (i.e., phencyclidine (PCP), ketamine, and N-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl- 4-isoxazole propionic acid (AMPA) receptors), which induces microglial activation, neuronal damage or death by excitotoxicity and in the end leads to the pathogenesis of numerous neuropsychiatric disorders such as schizophrenia, depression, autism, and neurodegenerative diseases (Reus et al. 2018). Notably, glutamate neurotransmission, including neurotransmitter synthesis, signaling, and glutamate receptor functions and expression seem to be involved in both stress vulnerability and resilience. Chronic stress decreased resilience and consequently the levels of glutamatergic neurotransmission of AMPA receptors, in animal models of depression (Li et al. 2018).

28.2.1.5 GABAergic Pathway

The γ-Aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain, progressively decreases during stress in animals (Zhang et al. 2016) and humans (Schür et al. 2016). Dysfunction of GABAergic neurotransmission is implicated in the development of stress-induced psychiatric disorders in both clinical and preclinical research (Jacobson et al. 2007; Albrecht et al. 2017). Notably, GABAergic neurons in the nucleus accumbens of the limbic system are correlated with the resilience and vulnerability to chronic stress for major depression (Zhu et al. 2017). Interestingly, the $GABA_{B(1)}$ subunit is expressed as different isoforms, and in the brain the predominant isoforms are $GABA_{B(1a)}$ and $GABA_{B(1b)}$. These isoforms, $GABA_{B(1a)}$ and $GABA_{B(1b)}$, exhibit differential cognitive and conditioned fear responses and regulate stress resilience or vulnerability to psychiatric illness in animal models (O'Leary et al. 2014). Several lines of evidence suggest that upregulation of the $GABA_A$ receptor α1 subunit in the ventral hippocampus increases resilience in animal models of juvenile stress and can lead to the development of stress-related psychopathologies (Ardi et al. 2019). The impact of basolateral amygdala activation on synaptic plasticity in the hippocampus, under conditions of heightened stress, induces alterations in the GABAergic system in limbic and prefrontal cortical areas. Thus, reducing GABAergic inhibition of specifically the axon initial segment of principal neurons within the basolateral amygdala represents a protective factor against traumatic stress on hippocampus-dependent cognitive and plasticity functions in rats (Saha et al. 2018).

28.2.2 *Mitochondrial Resilience*

It is well established that genetic predispositions, epigenetic changes as well as various environmental influences (comprising adverse life events such as childhood maltreatment, migration, or chronic stress) contribute to mental illness vulnerability. Mitochondrial stress occurring in response to many oxidative injuries, impairment of energy metabolism and calcium homeostasis that initiates apoptotic cytochrome C release is associated with mitochondrial dysfunction and neurodegeneration (Mosconi et al. 2011). On the other hand, mitochondria dynamically interact with each other and respond to different stressors to generate signals of resilient adaptation. Within the cell, mitochondria are in close proximity to the cell nucleus and, in response to environmental signals, undergo dynamic, morphological and functional changes leading to the production of biochemical signals to which the cell and its plastic epigenome evolved molecular sensitivity (Picard et al. 2013; Shaughnessy et al. 2014; Houtkooper et al. 2013). Recently, studies have in fact demonstrated the existence of a functional crosstalk between mitochondria and nuclear epigenome as a new aspect of bidirectional mito-nuclear communication: mitochondria are essential mediators of epigenetic processes and, conversely, changes in the epigenome regulate mitochondrial function. Consequently, their functions are fundamental aspects of cellular health (Matilainen et al. 2017). Accordingly, recent studies of gene-stress-interaction demonstrated that downregulation of *cacna1c* gene expression promotes mitochondrial resilience against oxidative stress in neuropsychiatric disorders (Michels et al. 2018). Mitochondria synthesize and metabolize AQ1 stress hormones (i.e., glucocorticoids and catecholamines). It is interesting to note in the context of stress resilience that stress hormones display a biphasic role in regulating mitochondrial function, i.e., a hormetic mechanism. An integrative view of chronic stress targeting mitochondrial bioenergetics thus opens new opportunities to study mechanisms of resilience adaptation across the lifespan.

Consistent with this concept, mitochondria regulating energy homeostasis and brain resilience adaptation processes represents a major marker of brain health (Picard et al. 2018a). Importantly, chronic stress induces mitochondrial damage and dysfunction in various brain regions, with impairment of neurotransmission underlying development and progression of neurodegenerative and neuropsychiatric pathogenesis. Moreover, prolonged exposure to glucocorticoids causes respiratory chain dysfunction, increased ROS generation, mitochondrial structural abnormalities, apoptosis and cell death in skeletal muscle cells and hippocampal neurons (Picard et al. 2018a). In light of this, glucocorticoids should be regarded as *mitokines*, i.e., mitochondria-derived hormones, mediating mitochondria-to-mitochondria communication among distant sites throughout the organism (Picard et al. 2018b). Notably, moderate mitochondrial stress can enhance mitochondrial antioxidant capacity through upregulation of antioxidant enzymes and, hence, increase resilience to metabolic stress (Lee et al. 2010), with impact on lifespan in mice (Schriner et al. 2005).

28.2.3 *Regional Specificity of Brain Resilience and Vulnerability to Stress: A Neuroimaging Approach*

In recent years, neuroimaging techniques have become an increasingly important tool to study neural correlates of adaptive and non-adaptive behavior. Neuroimaging studies, such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), provided substantial evidence of both brain structure and function in supporting vulnerability or resilience to stress in different neurological disorders.

Resilience is associated with morphological changes of brain regions involved in cognitive and affective processes related to the cortico-limbic system and plays an essential role in preserving mental function and physiological trajectories of brain network. In this context, higher levels of resilience are related to distinct morphological alterations in brain regions involved in executive control and emotional arousal networks, suggesting individuals with low resilience may have compromised cortico-limbic inhibition, making them more vulnerable to stress or trauma (Gupta et al. 2017).

Interestingly, the connectivity of these brain regions modulates resilience and vulnerability processes during stress or brain trauma (i.e., early life trauma, childhood maltreatment) (McEwen et al. 2016a). Accordingly, these brain regions are implicated in the storage of cognitive control, memory consolidation, neurogenesis as well as emotion regulation (McEwen et al. 2016b). The structural changes in the brain induced by chronic stress play a critical role in the pathophysiology of both neurodegenerative and neuropsychiatric disorders in animal and humans (Ebertowska et al. 2020; Kawaike et al. 2019). In addition, alterations observed in the cytoarchitecture of the hippocampus and amygdala have been related to stress resilience and vulnerability in animal models of PTSD (Cohen et al. 2014).

In humans, several studies demonstrated that chronic stress or traumatic experiences in childhood maltreatment (i.e., parental neglect, early deprivation, physical, sexual and emotional abuse) are associated with morphological alterations in specific brain regions. Specifically, there is increased atrophy of neurons in the hippocampus, prefrontal and parietal cortex, involved in memory, selective attention, and executive function (Bremner et al. 2005; Gupta et al. 2017). Similarly, these negative events cause hypertrophy of neurons in the amygdala involved in emotional processing and arousal, fear conditioning, anxiety and aggression as well as diminished striatal response to anticipated reward. This leads to increased vulnerability and development of neuropsychiatric and neurodegenerative illness (Guo et al. 2018). Moreover, animal studies have shown smaller amygdala volumes associated with lower levels of resilience, in keeping with neuroimaging findings demonstrating that amygdala volume is reduced in individuals who have been exposed to early adverse life events or maltreatment. For example, smaller amygdalae have been observed in individuals undergoing conditions of childhood poverty (Luby et al. 2013), as well as in adolescents having experiences of childhood maltreatment (Edmiston et al.

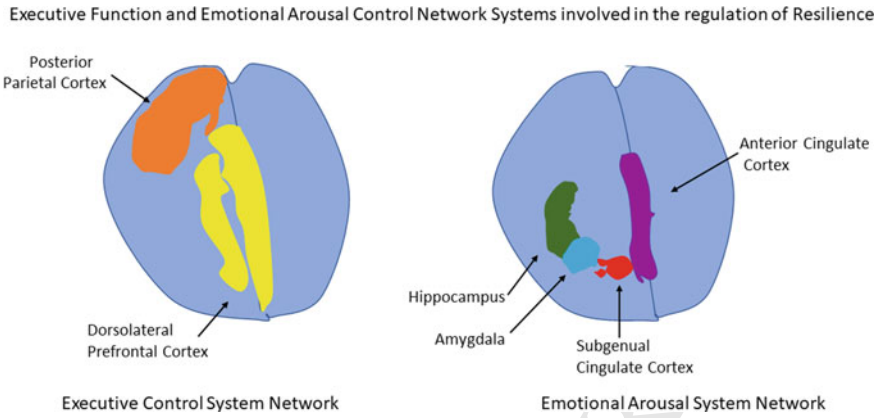

Fig. 28.3 Regions involved in the executive control and emotional arousal functions. Executive Control Network System: Dorsal-lateral Prefrontal Cortex, Posterior Parietal Cortex. Emotional Arousal System Network: Anterior Cingulate Cortex, Subgenual Anterior Cingulate Cortex, Amygdala and Hippocampus

2011). Smaller amygdala volumes have been also observed in individuals exposed to childhood adversities such as physical abuse, neglect, or being raised in poor households (Hanson et al. 2015) and in PTSD populations compared to healthy controls (Depue et al. 2014). These studies indicate that impaired executive control and emotional arousal networks in critical cortico-limbic structures, such as the dorsal-lateral prefrontal cortex, posterior parietal cortex, and respectively anterior cingulate cortex, anterior mid-cingulate cortex, subgenual anterior cingulate cortex, amygdala and hippocampus, show inhibition in response to trauma, suggesting that they may play a critical role in the mediation of low resilience or vulnerability to disease (Fig. 28.3).

Moreover, a recent study demonstrated that glucocorticoid receptor stimulation by early maternal stress and long-term gene expression changes induced aberrant DNA methylation in prefrontal cortex of rats (Urb et al. 2019). A few neuroimaging studies have investigated the response to adversity as a "proxy" of resilience, reporting quite important resilience-related differences in brain structure (DeYoung et al. 2010). Retrieval of emotionally-valenced words in females with histories of early abuse has been linked to decreased blood flow in the inferior parietal cortex (Bremner et al. 2003). In an emotional Stroop task, there was decreased parietal cortex activity in females with histories of PTSD and abuse (Bremner et al. 2004). The parietal cortex is a key region of the executive control network, and is associated with inhibitory control, attention, working memory, planning, and response (Uddin et al. 2011). Therefore, the findings are consistent with the hypothesis that high resilient individuals may be better able to engage the executive control network, including its role in inhibitory functions in relation to real or perceived challenge to their homeostasis.

The emerging links between neurogenesis and mental health support the idea that improving resilience represents a neurogenic strategy to treat patients suffering

from major depression, schizophrenia, and neurodegeneration (Apple et al. 2017). Neurogenesis plays a critical role in the synaptic plasticity of brain functions, such as olfactory discrimination, memory formation, and fear extinction (Shors et al. 2001; Alonso et al. 2006; Pan et al. 2012). In this context, it has been reported that stressful or traumatic events induce glucocorticoid release and decrease adult hippocampal neurogenesis (Snyder et al. 2011). Animal studies of early maternal and social deprivation reveal stress enhanced neurogenesis in the dentate gyrus of the hippocampus and in the amygdala. In fact, mice exposed to early life stress exhibited a reduction in amygdala/hippocampus-dependent fear memory because they have reinforced stress resilience to cope with future stressors and maintain a normal homeostatic state (Daun et al. 2020). Accordingly, dysfunction of adult neurogenesis enhances vulnerability of the hippocampus, and development of age-related neurodegenerative diseases, as well as neuropsychiatric diseases. On the contrary, enhancing neurogenesis confers resilience to stress by regulating the processing of both cognitive and emotional functions. Animal studies reported that increasing hippocampal neurogenesis promotes resilience to chronic social defeat stress by moderate exercise (Nguemeni et al. 2018) and inhibiting ventral dentate gyrus (Anacker et al. 2018). Brain imaging data of the hippocampus in patients and stress-induced animal models with either depression or anxiety disorders indicated a remarkable reduction in region volume and dendritic spine numbers. By contrast, larger hippocampal volumes could be a biological marker of resilience, whereas, loss of hippocampal neural plasticity (e.g., loss glial cell and smaller neuronal cell nuclei) after chronic stress is a determinant factor to the pathophysiology of depression in vulnerable human and animal models (Park et al. 2019; Carboni et al. 2018).

Additionally, a recent report suggested that hippocampal proteomic changes are associated with protein alterations involved in mitochondrial and metabolic pathways and lead to increased vulnerability or resilience to stress-induced depression and anxiety in stressed rats (Tang et al. 2019). Recently, several studies have correlated increased amygdala reactivity as a protective factor that promotes resilience to depression following early life stress (Yamamoto et al. 2017). In contrast, others studies have revealed that high emotional resilience is associated with lower levels of connectivity in the ventral amygdala network independent of depression status. Instead, lower depression symptoms were associated with higher connectivity between the amygdala and dorsal frontal networks in older adults (Leaver et al. 2018). In addition, repeated stress induces a pro-inflammatory state by increasing the amygdala's neuronal and microglial activation, which triggers anxiety-like behaviors in rodents (Munshi et al. 2020).

Taken together, these data showed brain network connectivity in the main brain regions such as hippocampus, amygdala as well as prefrontal and parietal cortex in response to stress or trauma and how neural factors are involved in increasing resilience or vulnerability after stressful events across the lifespan. A history of stress exposure can have a lasting impact on future stress reactivity in different brain regions. Finally, the elucidation of brain region alterations will undoubtedly lead to more effective and better tolerated treatment approaches to enhance resilience and its use as a potential biomarker of healthier adulthood adaptations to childhood trauma.

28.3 Plant Polyphenols Improve Resilience and Brain Health via "Vitagenes"

Emerging research has focused on brain resilience, for neuroprotection, elicited by plant polyphenols through the activation of the Nrf2-vitagene signaling pathway (Figs. 28.1 and 28.2). The latter encodes redox sensitive genes, such as heme oxygenase-1 (HO-1), heat shock proteins (Hsps), thioredoxin and sirtuin system, termed vitagenes which are involved in preserving brain health and cellular homeostasis in response to stress or trauma in major neuropsychiatric and neurodegenerative disorders (Calabrese et al. 2010; Trovato et al. 2014, 2016a). Increasing evidence suggests that plant polyphenols (i.e., resveratrol, hydroxytyrosol, oleuropein, sulforaphane, curcumin, as well as gingko biloba) may exert healthy benefits acting in a hormetic-like manner through the modulation of vitagenes, making the hormesis concept fully applicable to the field of nutrition (Scuto et al. 2019a, b; Amara et al. 2020a; Trovato et al. 2016b, 2018; Calabrese et al. 2014, 2018a).

Interestingly, recent in vitro and in vivo studies suggest that Hydroxytyrosol (HT) and Oleuropein (OLE) inhibit the inflammatory response and induce brain resilience to aging process through different pathways regulated by several members of the sirtuin family (e.g., Sirt1, Sirt2, Sirt3 and Sirt6) (Leri et al. 2020; Zhi et al. 2018; Gallardo-Fernández et al. 2019; Corpas et al. 2019a). The thioredoxin system (Trx/TrxR) is an important thiol/disulphide redox controller ensuring the cellular redox homeostasis and resilience to mental illness (Calabrese et al. 2012; Amara et al. 2020b; Dang et al. 2019). In this context, some studies showed that HT induces neuroprotection and cellular antioxidant defenses via activation of the Keap1-Nrf2-TRXR1 pathway (Peng et al. 2015).

Sulforaphane is an herbal isothiocyanate enriched in cruciferous vegetables obtained in high concentrations from broccoli seeds and sprouts. Recently, it has been reported that sulforaphane induces health benefit by upregulation of Nrf2 pathway against oxidative stress and inflammation in prenatal prevention of autism spectrum disorder as well as for the early treatment of young children with this disorder (Nadeem et al. 2019). Preclinical studies suggested that intake of 0.1% sulforaphane during juvenile and adolescence protect against inflammation and stress depression-like behaviors via Nrf2 signaling and confers stress resilience in adulthood (Yao et al. 2016). Moreover, a recent paper has suggested that lower levels of BDNF-Nrf2 pathway are strongly associated with oxidative stress and vulnerability to depression in rats. On the other hand, activating Nrf2 translocation restored redox homeostasis and induced resilience to stress (Bouvier et al. 2017).

Several studies have reported the antioxidants, anti-inflammatory and cognitive resilience properties of resveratrol (3,5,4′-trihydroxy-trans-stilbene), a polyphenol found in red wine presently under clinical trial against neuropsychiatric and neurodegenerative disorders. Recent compelling evidence indicated that resveratrol improves brain resilience and proteostasis through the activation of Sirt1 pathway against amyloid and tau pathologies caused by accumulation of aberrant proteins in AD

mouse models as well as in lymphocytes of AD patients (Corpas et al. 2019b; Cosìn-Tòmas et al. 2019). Curcumin is a polyphenol compound extracted from the rhizome of *Curcuma longa Linn* (family Zingiberaceae) commonly used as a spice to color and flavor food. Increasing evidence demonstrated that curcumin promotes resilience and may prevent the emergence of a range of anxiety-like symptoms in individuals during exposure to chronic social stress (Aubry et al. 2019) as well as depression-like behaviors in rats (Huang et al. 2011). Recently, Ginkgo biloba extracts showed effectively as an alternative medicine for treatment and prevention of neurodegenerative and neuropsychiatric illness and acts in a hormetic-dose response manner (Calabrese et al. 2020). Moreover, several studies reported the beneficial effects of Ginkgo biloba extracts in modulating fear memory retrieval through serotoninergic, GABAergic, and glutamatergic receptors in the dorsal hippocampal formation, by enhancing cognitive function and resilience in psychiatric disorders (Gaiardo et al. 2019). Taken together these data indicate that brain resilience is an active protective process that involves a set of neural and cellular mechanisms leading to avoid some of the negative consequences of excessive stress therefore improves mental health.

Finally, in the field of neuroprotection, moderate and chronic consumption of low doses of plant polyphenols could be considered as a promising "natural preventive medicine" which confers resilience through the activation of stress responsive *vitagenes*. By activating neuroprotective cascades such interventions could be effective to prevent neuroinflammation, promote brain resilience and improve brain health in aging-related cognitive decline as well as in neuropsychiatric disorders in humans.

28.4 Conclusions

Aging is one of the most challenging public health issues and it is considered as a "cellular danger response" to environmental stressors or injury leading to the development of neurodegenerative disorders. Emerging research has focused on how biological resilience may be elicited by consumption of phytonutrients, particularly vitamins and plant phenols. These interfere with multiple signaling pathways involved in protein homeostasis, DNA repair, metabolism regulation, and antioxidant defenses in response to environmental stressors. Accordingly, the prevalence of harmful stressful events, or so-called "black swans," may contribute to establishing a particularly resilient or vulnerable endophenotype.

Resilience comprises different physiological parameters, epigenetic modulators and neurobiological markers. In this review, we have provided a brief overview of some biological mechanisms underlying stress resilience and have explored how resilience changes throughout age. The neurobiological network represented by the HPA axis, BDNF, Serotonin, Glutamate and GABAergic pathways operate as the first line of response to stress or challenges by promoting resilience and preserving mental health against the onset of brain disorders such as depression and anxiety, but they also slow neurodegeneration across the lifespan in both human and animal models. Epigenetic mechanisms are a key to understanding the effects of early stress

in childhood, such as poverty, maltreatment, maternal social and nutritional deprivation, familial genetic as well as sexual abuse. In light of this, identifying personalized biomarker signatures of resilience can help us characterize biologically vulnerable individuals (e.g., maltreated children). Relevant to this, psychobiological challenge tasks designed to evoke a resilient behavioral response, neuromodulation strategies visualized by neuroimaging of circuits that mediate resilience, together with antioxidant interventions enhancing resilience, are all fundamental preventive strategies aimed to operationalize resilience as a multifactorial determinant of brain health for translation into a clinical setting. Finally, neural signaling pathways activated by healthy lifestyles, such as moderate physical exercise, caloric restriction, intermittent fasting, heat shock response and antioxidant polyphenols, can also stimulate mitochondrial biogenesis in neurons in the brain, thereby facilitating neuroplasticity and hormetic-resilience pathways that modulate aging and longevity in humans.

Further studies are necessary, however, to evaluate the real importance of the neurobiological mechanisms impacting on target genes, as well as on epigenetic and mitochondrial pathways in specific brain regions. These studies will help to elucidate resilience factors, which promote brain health in response to stress, and to unravel the potential therapeutic interventions able to effectively increase resilience and improve stress management in vulnerable populations. AQ2

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Chapter 28

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