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REVIEW ARTICLE

Neurobiological Mechanisms of Stress Resilience and Implications for the Aged Population

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Abstract: ***Background*:** Stress is a common reaction to an environmental adversity, but a dysregulation of the stress response can lead to psychiatric illnesses such as major depressive disorder (MDD), post-traumatic stress disorder (PTSD), and anxiety disorders. Yet, not all individuals exposed to stress will develop psychiatric disorders; those with enhanced stress resilience mechanisms have the ability to adapt successfully to stress without developing persistent psychopathology. Notably, the potential to enhance stress resilience in at-risk populations may prevent the onset of stress-induced psychiatric disorders. This novel idea has prompted a number of studies probing the mechanisms of stress resilience and how it can be manipulated.

***Methods*:** Here, we review the neurobiological factors underlying stress resilience, with particular focus on the serotoninergic (5-HT), glutamatergic, and γ-Aminobutyric acid (GABA) systems, as well as the hypothalamic-pituitary axis (HPA) in rodents and in humans. Finally, we discuss stress resiliency in the context of aging, as the likelihood of mood disorders increases in older adults.

***Results*:** Interestingly, increased resiliency has been shown to slow aging and improved overall health and quality of life. Research in the neurobiology of stress resilience, particularly throughout the aging process, is a nascent, yet, burgeoning field.

***Conclusion*:** Overall, we consider the possible methods that may be used to induce resilient phenotypes, prophylactically in at-risk populations, such as in military personnel or in older MDD patients. Research in the mechanisms of stress resilience may not only elucidate novel targets for antidepressant treatments, but also provide novel insight about how to prevent these debilitating disorders from developing.

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1. INTRODUCTION

Brain disorders and particularly psychiatric disorders, comprising affective disorder [major depression (MDD), and anxiety disorders [panic disorders (PD) with and without agoraphobia, generalized anxiety disorder (GAD), panic bipolar disorder (BP), and cyclo- and dysthymic disorders] or social phobias, PTSD and obsessive-compulsive disorder (OCD)] are among the leading causes of disease and disability in the world. MDD was ranked as the fourth leading contributor to the global burden of disease and is the leading cause of disability worldwide as measured by Years Lived with Disability (YLDs) [1]. Mental disorders amounted to €240 billion and hence constitute 62% of the total annual cost of brain disorders in Europe [2]. In the United States, the total annual cost of depressive disorders was estimated to be $83.1 billion [3] and more than $42 billion for anxiety disorders [4], among the most prevalent mental disorders.

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Since the 2000s, an increasing prevalence of mental health problems, and consequently an increasing annual financial burden, has spurred an investigation into brain mechanisms of resilience that may protect against the development of psychiatric disorders.

In this review, we will first describe the psychosocial and neurobiological factors that contribute to stress resilience in rodents, nonhuman primates, and humans. The effects of stress throughout aging will then be discussed, as well as the potential risk factors and biological changes that increase susceptibility to mood disorders in older populations. There is an emerging field of research focused on resilience in the context of aging, as several studies have shown that the risk for developing mood disorders, particularly anxiety disorders, is increased with age [5-7]. Current behavioral methods to improve resilience in the aged will be considered, as well as suggestions for novel possibilities of fostering resilient phenotypes in this population and throughout life based on pre-clinical studies. Though these avenues of resilience enhancement are still in their infancy, there is great potential to refine these techniques to be administered to individuals who are most susceptible to stress, particularly as they age, in order to increase resiliency and prevent stress-induced disorders from occurring at any point in one's lifetime.

2. DEFINITION OF RESILIENCY

An external, unexpected stressor can induce a normal physiological and behavioral stress response. This normal and basic response resulting in an organism's adaptive capacity is characterized by activation of the hypothalamic-pituitary-adrenal (HPA) axis, with a relative peak of serum cortisol or corticosterone 30 minutes following stress exposure, followed by a quick recovery either in human or rodent, in 60-80 minutes after the stress [8, 9]. But prolonged exposure to stressful events (*i.e*., over weeks) can lead to chronic stress and persistent sequelae, depending on the ability of each person to adapt to potent stressors. Indeed, individuals perceive stressful events differently, and when the stress response becomes overactive, the recovery mechanisms fail to achieve, leading to increased susceptibility to stress. Yet, 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 such MDD or anxiety disorders. Conversely, people who are able to effectively develop well socially, mentally or physically despite exposure to stress or adversity demonstrate resiliency; elucidating the underlying mechanisms of this resilience may lend insight into methods to prevent mood disorders in susceptible individuals.

3. PSYCHOSOCIAL FACTOR-ASSOCIATED STRESS VULNERABILITY AND RESILIENCY

It is well established that the combination of genetic predisposition, familial heritage, socio-environmental factors, early life stress (ELS), and chronic illness or treatment largely determine vulnerability to psychiatric disorders such as MDD or anxiety disorders (Fig. **1**). Whereas stressful life events such as the loss of a loved one are related to the development of MDD and GAD, combat-associated injury and traumatic experiences are associated with the development of PTSD. Since the majority of people who experience such stressful events do not develop psychopathology, increasing interest has been directed at potential resilience factors that may provide mental resistance. Developing novel therapeutics targeted at these factors is one avenue to decrease the incidence of mental illnesses.

The idea that increasing stress resilience could protect against the development of psychiatric disorders is appealing. Currently, five basic psychosocial resilience factors where listed based on enormous body of published research: positive emotions and optimism, cognitive flexibility, religion and spirituality, life meaning, social support and active coping style to be protective psychosocial factors that have been associated with stress resilience [10]. A study using a sample of 200 post-doctoral fellows indicated that resilience moderated the impact of stress on trait depressive and anxiety symptoms [11]. Besides revealing a positive association between positive emotions and resilience, this study also indicated that coping strategies partially mediated the link between positive emotions and resilience [11]. Moreover, findings from a prospective longitudinal study provide evidence that individual differences in stress resilience are predicted by both lower levels of negative emotions and higher levels of responsiveness in a positive direction before

Fig. (1). Factors associated with stress-induced emotional disorders and those believed to characterize stress resilience. Combination of psychosocial environment, genetics and early life stress largely determine vulnerability to MDD and anxiety disorders. In contrast, the strategy to improve positive emotions, cognitive flexibility, optimism and active coping leads to promote stress resilience.

stressor exposure [12]. Overall, these findings suggest that coping strategies are essential to minimize the impact of stress.

The coping strategies that have been studied so far have focused their efforts on adolescent and youth populations. For instance, the Protection for Adolescent Depression Study (PADS) developed a vulnerability-resilience stress model for mood disorders, based on the principle that vulnerability and resilience in the face of stress inform an accurate prediction of psychopathology [13]. Using this model in a cohort of 283 healthy adolescents and 119 from a mood disorder clinic, they found two productive coping strategies-focusing on the positive and working hard to achieve-which moderate the impact of stress and predict lower levels of light-to-severe depression and suicidal behavior. Interestingly, girls who focused on the positive were more protected than boys against light-to-severe depression. Finally, self-discovery from the spirituality scale was the only protective factor in the community and reached the significance level only for boys in the clinical population. Thus, this study suggests targeting different factors for men and women to increase or restore protection in the presence of chronic stress conditions. The Early Prediction of Adolescent Depression (EPAD), a longitudinal study of parents with a history of recurrent MDD and their high-risk adolescent offspring, provide evidence that higher executive functioning, such as inhibition and mental flexibility, may confer protection against depressive symptoms to the adolescent offspring of depressed parents as compared to adolescents with poorer performance on these measures [14].

4. PERSONAL STRATEGIES FOR BUILDING STRESS RESILIENCE

Since it was reported that resilient individuals showed an increase in protective psychosocial factors, a group psychosocial resilience-training program was developed to promote resilience and psychosocial well-being in adults who are at risk for stress-induced depressive symptoms, but are otherwise generally healthy. The REsilience and Activity for every DaY (READY), targeting positive emotions, problem solving, life purpose and cognitive flexibility, demonstrated favorable intervention effects on measures of cognitive flexibility (acceptance and mindfulness), environmental mastery, positive emotions and personal growth, as well as moderate effects on measures of stress, self-acceptance, valued living and autonomy [15]. Other studies investigating the effectiveness of resilience training showed positive change occurring at post-intervention compared with baseline or control group [16, 17].

Further, regular exercise is frequently associated with general well-being and lower rates of mood disorders, probably in enhancing resilience to stress. Indeed, among young healthy men and women, individuals who exercise regularly showed smaller decline in positive affect after an acute stressor than those who did not reported regular physical exercise [18]. These findings suggest that regular exercisers are more resistant to the emotional effects of acute stress and might protect them against diseases related to chronic stress burden.

Overall, resilience is an active process that involves a set of neural and cellular mechanisms leading to avoid some of the negative consequences of extreme stress in individuals. The social environmental as well as the genetic and the biological backgrounds of an organism fundamentally influence the balance between risk and resilience to stress (Fig. **1**). Nevertheless, the identification of biological resiliency factors for mood disorders is an important challenge facing biological psychiatry today and the key leading to the development of new pharmacologic treatments for preventing mental illnesses.

5. NEUROBIOLOGICAL FACTORS IN STRESS RESILIENCE

While there has been extensive research on psychosocial factors promoting susceptibility or resilience to psychiatric illnesses, studies published on genetic or biological mechanisms of human resilience are still in their infancy. The development of animal models is necessary not only to appreciate the various aspects of human pathology, such as physiological or behavioral changes, but also to understand the dynamics of therapeutic effects. It is therefore essential to evaluate mechanisms underlying stress resilience processes in animal models expressing symptoms of anxiety-depression pathologies.

6. RODENTS-ANIMAL MODEL OF STRESS RESILIENCY

Despite the complexity in designing and validating animal models in psychiatric research, the animal models [chronic mild stress (CMS), social defeat (SD), learned helplessness (LH), prenatal restraint stress, maternal separation and daily corticosterone administration (CORT)] we have chosen to use in this review were developed and are most often used to model affective disorders relevant to humans, as well as to screen a large panel of molecules with putative anxiolytic- and antidepressant-like activities. These models showed predictive validity in terms of depression or anxiety. However, even though they are inbred strains, a remarkable inter-individual variation in developing anxio-depressive symptoms has been noted. Recognizing the existence of this variation led to the classification of susceptible versus resilient animals that have varying degrees of depressive or anxiety. Work in animal models has suggested that stress resilience is mediated through active neurobiological processes, and has identified a number of protective psychosocial factors.

7. THE SEROTONERGIC SYSTEM

7.1. The Tryptophan Hydroxylase (TPH)

Tryptophan (TRP) is the precursor of peripheral and central serotonin (5-HT) synthesis. Thus, low TRP leads to low 5-HT levels, which contributes to mood state impairments and induces stress vulnerability (reviewed in [19]). Indeed, TRP-depleting drink administration-induced 5-HT depletion made healthy volunteers more susceptible to the effects of uncontrollable stress. These subjects showed more robust negative mood responses, particularly in sadness-related ratings, compared with TRP-supplemented group [20].

5-HT is produced from TRP *via* the rate-limiting enzyme TPH, which exists in two different isoforms. Whereas TPH1 mRNA is mainly expressed in peripheral tissues and in the pineal gland, the TPH2 isoform gene, recently discovered, is predominantly expressed in the brain. Although TPH2 is mainly responsible for the synthesis of brain 5-HT, studies to establish an association between the TPH2 gene and psychiatric disorders or stress resilience are still under investigation. One study demonstrated that in male Tph2 knockout (KO) mice, which completely lacked brain 5-HT synthesis while 5-HT raphe neurons remained functional, the 5-HT deficiency resulted in reducing anxiety-like behavior in the elevated plus maze (EPM) and open field (OF) [21] (Table **1**). Discrepant results were reported for gene-by-environment interactions (GxE). A 3-week CMS was deleterious in Tph2 KO mice resulting in anxiety-like behavior in the EPM, but surprisingly, 5-HT dysfunction provided protective effect against chronic mild stress (CMS) in the OF [21] (Table **1**).

From a clinical perspective, it appears counterintuitive that 5-HT deficiency results in anxiolytic effects, but similar results were found in resilient rats exposed to ELS [22]. Indeed, when MS15 rats, which are normally used as a model of decreased stress sensitivity**,** were subjected to a 10-day social defeat (SD) experience, the mean of Tph2 mRNA expression throughout the dorsal raphe nucleus (DRN) was decreased and conversely, MS180 rats, regarded as a model of vulnerability to depressive-like symptoms, elicited a two-fold increase in Tph2 mRNA as compared to MS15 rats [22] (Table **1**). Interestingly, effects of ELS on Tph2 mRNA expression were only apparent in rats exposed to SD during adulthood [22]. These data suggested that MS15 resilient rats are resistant to SD-induced changes in Tph2 mRNA expression. However, it is important to note that this study lacks a complete behavioral analysis and that the mRNA results should be correlated with the measurement of social interaction in defeated rats. Moreover, these data contradict those obtained in highly stress-resilient (HSR**)** cynomolgus monkeys submitted to a 5-day exposure of a combined moderate stress paradigm. It has been shown that the HSR group had significantly higher average Tph2-positive cells than the stress sensitive (SS) group, suggesting that an upregulation of serotonin-related genes is protective against stress (Table **1**). Unfortunately, no comparison with control animals was made in this study. In conclusion, TPH impairment leading to decreased brain 5-HT synthesis subsequently compromises one's ability to cope with uncontrollable stress.

7.2. The Serotonin Transporter (SERT)

The 5-HT transporter (SERT) gene (SLC6A4), another actor of the neurotransmission homeostasis, may play a modulating role in rendering individuals vulnerable or resilient to stress. A common polymorphism, resulting in insertion or deletion, called, respectively, long (l) and short (s) forms have been identified in the SERT gene-linked polymorphic region (5-HTTLPR) of the SLC6A4. It has been argued that individuals carrying two copies of the long-allele (l/l) are relatively protected against mood disorder development [23, 24], and have increased cognitive emotional control and higher inhibition of negative information [25]. Individuals with 1 or 2 copies of the short-allele (s/l or s/s) are less resilient, and exhibited increased depressive symptoms following stressful life experiences [26-28]. Yet, these alleles are fundamentally neutral because in the absence of stress, no direct association between the SERT gene and depression was observed among members of the Dunedin Multidisciplinary Health and Development Study [26]. Thus, instead of viewing the s-allele as a risk-allele for vulnerability and the l-allele as a protective-allele for resiliency, functional polymorphisms in the 5-HTTLPR was only predisposing to mood disorders when interacting with environmental stress factors. For example, a study in U.S. Army soldiers with no prior war zone exposition who were scheduled to deploy to Iraq confirmed that s-allele carriers, interacted with levels of stressful exposure to predict the development of PTSD, anxiety, and depressive symptoms [29].

In order to model the human allelic variation in SERT function and for a better understanding of its behavioral consequences, heterozygous SERT-deficient mice were generated. In the absence of stress exposure, SERT KO offspring displayed lower levels of anxiety in the elevated zero maze (EZM), and in addition, developed a resilient phenotype to prenatal restraint stress (PS), compared to wild-type (WT) offspring [30] (Table **1**). However, while, SERT KO offspring showed antidepressant-like behavior in the forced swim test (FST) compared to WT offspring, distance swum was decreased in restrained SERT KO offspring [30]. In this way, a decrease in SERT expression may protect against ELS. Indeed, SERT expression seems to be related to the levels of the vulnerability or resiliency of the animals. After isolating CMS-resilient animals, Couch and colleagues reported that unlike resilient mice, mRNA-encoding SERT was upregulated in vulnerable mice in the prefrontal cortex (PFC), striatum, and hippocampus, but not in the DRN [31] (Table **1**). Similarly, Zurawek and collaborators found significantly decreased SERT protein level in the ventral tegmental area (VTA), but not in the DRN or PFC of CMS-resilient animals as compared to anhedonic and control rats [32] (Table **1**).

With the idea still being that female macaques with different stress sensitivity exhibit different adaptive biological mechanisms from those set up in rodent in response to stress, the Bethea study also looked at the SERT-positive cell number in the DRN of HSR and SS female monkeys, but no difference was found [33]. Nevertheless, these results should be interpreted with caution, since this same team has earlier shown that although SERT mRNA are significantly lowered in non-stressed SS monkeys compared with non-stressed HSR monkeys in the caudal regions of the raphe [34], the ratio of the HSR/SS groups for the SERT gene was similar in the presence or absence of stress, implying that there is no adjustment in the 5-HT system after 5 days of moderate stress [33].

7.3. The Serotonin Receptors

5-HT released from serotoninergic neurons in the DRN throughout the brain modulates the acute stress response *via* its impact on a diverse group of serotonin receptors (for review, see [35]). Among the serotoninergic receptors, the 5-HT_{1A} receptor (5-HTR_{1A}), located either on the presynaptic (autoreceptor) or postsynaptic (heteroreceptor) terminals of

Table 1. Role of the different 5-HT pathway-related key players in the stress-vulnerability and resilience in animals.

	Species	Strain	Sex/Age	Model/Treatment	Stress	Duration	Results (*vs* Control)	Refs.
Tph2	Rat	Long Evans	♂ 10 weeks	Vulnerable (MS180 - maternal separation)	SD	12 days	Tph2 mRNA in DRN: ↑	Gardner *et al*., 2009
				Resilient (MS15 - early handling)			Tph2 mRNA in DRN: ↓	
	Monkey	Cynomolgus	♀ 7-9 years	Resilient (normal ovulatory cyclicity) (vs anovulatory vulnerable monkeys)	Mild psychosocial stress + mild diet ± moderate exercise	5 days	Tph2-positive cells in DR: ↑	Bethea *et al*., 2013
	Mouse	ND	♂ Adult	Tph2 KO	Ø	acute	SPT: ↑ EPM: ↓ time in CA, ↑ distance/entries in OA OF: ↑ time in center FST: no difference	Gutknecht *et al*., 2015
					CMS	3 weeks	EPM: ↑ time in CA OF: ↑ entries in center FST: no difference	
SERT	Mouse	B6.129(Cg)-Slc6a4tm1Kpl/J	♂ ND	Heterozygous 5-Htt KO	Ø		EZM: ↑ time/entries in OA FST: no difference	van den Hove *et al*., 2011
					Prenatal RS	5 days	EZM: ↑ time in OA FST: no difference	
	Rat	Wistar Han	♂ ND	Vulnerable (↓ sucrose consumption >20%)	CMS	2 weeks	SERT expression: no difference	Zurawek *et al*., 2016
				Resilient (no difference in sucrose consumption)			SERT expression: ↓ in VTA	
	Mouse	C57BL/6J	♂ 3.5 months	Vulnerable	CMS	10 days	SERT expression: ↑ in PFC, hippocampus, striatum	Couch *et al*., 2013
				Resilient (> 65% preference for sucrose)			SERT expression: no difference	
5-HT$_{1A}$	Mouse	mixed 129S6/Sv; C57B6; CBA	♂ 11-13 weeks	1A-Low mice (vs 1A-High mice)	Ø	acute	OF/LDT/TST: no difference FST: ↓ immobility 5-HT levels: no difference in PFC, hippocampus	Richardson-Jones *et al*., 2010
					Oral gavage	4 weeks	OF/FST: no difference TST: ↓ immobility	
	Monkey	Cynomolgus	♀ 7-9 years	Resilient (normal ovulatory cyclicity) (vs anovulatory vulnerable monkeys)	Mild psychosocial stress + mild diet ± moderate exercise	5 days	5-HT$_{1A}$-positive cells in DR: ↑	Bethea *et al*., 2013
Drugs	Rat	Lewis	♂ 8-9 weeks	Fluoxetine (7.5 mg/kg/d, 21 days)	SD		EPM: reverse defeat-induced ↓ entries/time in OA	Berton *et al*., 1999
	Mouse	129S6/SvEvTac	♂ 8-10 weeks	Fluoxetine (18 mg/kg/d, 21 days)	SD	2 weeks	EPM/FST: did not reverse defeat-induced ↑ time in CA and ↑ immobility	Brachman *et al*., 2016
	Mouse	C57BL/6NTac			CORT	3 weeks	EPM/NSF/FST/ST: did not reverse CORT-induced ↑ time in CA, ↑ latency to feed, ↑ grooming latency and ↑ immobility	
	Mouse	129S1/SvImJ	10 weeks	Escitalopram (4 mg/kg, 14 days)	CMS	14 days	HBT: ↑ time in center, ↓ head dipping FST: ↑ immobility	Binder *et al*., 2011

Abbreviations: 5-HT: serotonin; CA: closed arms; CMS: chronic mild stress; CORT: corticosterone; DR: dorsal raphe; EPM/EZM: elevated plus/zero maze; FST: forced swim test; HBT: hole board test; KO: knock-out; LDT: light/dark test; ND: non-determined; NSF: novelty suppressed feeding; OA: open arms; OF: open field; PFC: prefrontal cortex; SD: social defeat; RS: restraint stress; SERT: serotonin transporter; ST: splash test; SPT: sucrose preference test; Tph: tryptophan hydroxylase; TST: tail suspension test; VTA: ventral tegmental area.

5-HT neurons, is one of the main actors responsible for the therapeutic delay of SSRIs. For this reason, 5-HTR_{1A} has been a matter of interest for its role in the etiology of both anxiety and depression. Plenty of human genetic and imaging studies demonstrated that differences in regulation and binding potential of 5-HTR_{1A} are associated with depression and anxiety (reviewed in [36]). While many studies in humans report an association of the G variant of the C(-1019)G 5-HTR_{1A} promoter gene polymorphism with higher expression of 5-HTR_{1A} and higher susceptibility to depression, no studies have focused on the effect of carrying the C(-1019) allele on vulnerability or resilience to mood disorders. Recently, Lemonde and colleagues postulated that carrying the C(-1019) allele, unlike the G(-1019), leads to a marked decrease in 5-HT_{1A} mRNA, protein, and binding sites in the DRN, which could confer behavioral resilience to stressful situations [37]. Similarly, to provide a mechanistic model of one of the predicted consequences of the recently identified human Htr1a C(-1019)G polymorphism, a new strategy to manipulate 5-HT_{1A} autoreceptors in raphe nuclei without affecting 5-HT_{1A} heteroreceptors, generating mice with higher (1A-High) or lower (1A-Low) autoreceptor levels, has been performed [38]. Adult 5-HT_{1A}-Low mice with 5-HT_{1A} autoreceptor deficiency in DRN neurons as compared to 5-HT_{1A}-High mice, exhibited reduced susceptibility to daily mild stressors (gavage) in the tail suspension test (TST) but not in the FST [38] (Table **1**). However, in basal state, 1A-Low mice displayed less behavioral despair in the FST, suggesting an active coping mechanism to stress over time [38] (Table **1**). Overall, these data suggest that reduced 5-HTR_{1A} expression correlates with stress resiliency, even if opposite results in female monkeys were reported with higher 5-HT_{1A}-positive cell numbers in the DRN of HSR individuals [33, 34] (Table **1**).

5-HT_{2A} receptors (5-HTR_{2A}) were also implicated in pathophysiology of emotional disorders, since brain imaging studies revealed a decrease in 5-HTR_{2A} binding in cortical [39-41] and hippocampal [42, 43] regions of depressed patients, and an increase in 5-HTR_{2A} binding in the caudate nucleus of unmedicated patients with OCD [44]. Regarding the role of 5-HTR_{2A} in stress resilience specifically, the data remain poor. A 3-fold increase in 5-HTR_{2A} expression in the PFC of CMS-resilient mice relative to control mice have been reported, even though this change was also observed in the PFC of CMS-vulnerable mice, with no significant difference between resilient and vulnerable groups [31]. In addition, higher 5-HTR_{2A} binding was also observed in the cortex of CMS rats [45]. The difference reported between CMS-resilient and CMS-vulnerable mice was an increase in 5-HTR_{2A} expression in the striatum of susceptible compared to control mice, whereas resilient mice did not show any change [31]. However, Farhang and collaborators did not find any difference in levels of 5-HTR_{2A} in either cerebral hemispheres of resilient rats to CMS [46], indicating that the connection between these receptors and stress resilience is not well-established.

7.4. The Serotonin Antidepressants in Preventing Stress Resilience

Antidepressants are typically used to treat existing depressive symptoms, but chronic antidepressant treatment also protects against subsequent depressive episodes [47]. Clinical practices recommend a 6 to 24 month antidepressant maintenance therapy to prevent recurrence, once an acute episode and the continuation treatment phase are over [48]. Placebo-controlled, double blind and randomized studies designed in patients with unipolar major depression demonstrated the efficacy of fluoxetine (20 mg/d) for the prevention of new depressive episodes, since treated patients were symptom-free for a longer period of time than patients assigned to placebo [49, 50]. In the same way, one-year treatment with paroxetine (20-30 mg/d) was effective in preventing the reappearance of depression for one year in depressed patient with more than two previous episodes in the preceding four years [51]. Citalopram (20 or 40 mg/d) treatment for 24 weeks in patients with MDD provided evidence for preventing relapse as compared to placebo [52]. Additionally, a 52-week treatment with sertraline in depressed patients conferred significantly greater prophylaxis against depression relapse and recurrence than did placebo [53]. In order to evaluate the efficacy of the different SSRIs in relapse prevention and prophylaxis of depression, Peselow and colleagues conducted a 3-year follow-up of MDD patients who had initially responded to SSRIs. Escitalopram and fluoxetine had the highest numerical prophylactic efficacy with 36% and 33.3% of the patients remained recurrence-free, respectively, although these differences were not statistically significant [54]. These results confirm the potential benefit of long-term pharmacotherapy for treating depressive illness.

However, one critical question emerges from these studies on the potential protectiveness of SSRIs: would these drugs confer similar prophylaxis if administered to healthy patients who are at-risk for developing mental illnesses such MDD or anxiety disorders? For example, fluoxetine (7.5 mg/kg/d, 21 days) pretreatment before SD seemed to prevent the defeat-induced anxiety-like behavior in Lewis rats, a highly stress-sensitive strain [55] (Table **1**). However, these results must be interpreted with caution, since no comparison was made between defeated rats pretreated with vehicle and defeated rats pretreated with fluoxetine. Moreover, chronic fluoxetine (20 mg/kg/d, 14 days) treatment in C57BL/6J non-stressed mice has been shown to suppress depression-related behaviors in the TST, but impair anxiety and stress-coping ability in the EPM and in the OF [56]. Recently, it was demonstrated that administration of fluoxetine (18 mg/kg/d, 3 weeks) before the start of SD in 129S6/SvEvTac mice did not consistently protect against stress-induced depressive- and anxiety-like behavior, respectively, in the FST and in the EPM [57] (Table **1**). However, fluoxetine pretreatment (18 mg/kg/d, 3 weeks) in C57BL/6NTac mice prevented the CORT-induced immobility in the FST, but did not protect against CORT-induced depressive- and anxiolytic-like behavior in the other paradigms [57] (Table **1**). These latest results may be related to the antidepressant-like effects of fluoxetine more than a prophylactic effect, since the FST has originally been developed to screen drugs based on acute administration before the swim stress. Systemic administration of escitalopram (4 mg/kg/d, 14 days), concurrent with a CMS procedure in 129S1/SvImJ mice, prior to testing in the hole-board test (HBT) appeared to increase the time spent in the center of the hole-board, which is assumed to be aversive

to rodents, but reduced the number of head dipping compared with saline-treated mice, which may reflect anxiogenic behavior [58] (Table **1**). Moreover, escitalopram failed to reverse the depressive-like symptoms induced by CMS; rather, it increased immobility in the FST in treated stressed mice compared to non-treated stressed mice [58] (Table **1**). In conclusion, prophylactic SSRI administration, at least in rodents as a protective strategy for stress-induced anxiety/depression-like behavior, is not fully efficient, but as we will describe later, other drugs may be more useful.

8. THE GLUTAMATERGIC SYSTEM

8.1. The *N*-methyl-D-aspartate (NMDA) Receptor

In the early 1990s, the glutamatergic pathway emerged as one of the most promising approaches for developing new antidepressant therapies, since an acute N-methyl-*D*-aspartate (NMDA) receptor blockade has been shown to improve behavioral deficits induced by inescapable stressors in NIH-Swiss and C57BL/6J mice [59]. Several years later, postmortem and magnetic resonance spectroscopy (MRS) studies reported region-dependent findings concerning glutamate or glutamine levels in MDD and BP patients, with higher levels in the frontal [60] and occipital [61] cortices and lower levels in the prefrontal [62, 63] and the anterior cingulate cortices [64, 65]. The literature so far provides contradictory results for glutamate levels in the hippocampus [66-68]. In rodents, exposure to stress produced an increase in glutamate release in regions mediating emotional behavior, as measured by intracerebral microdialysis [69]. In regards to specific glutamate receptors, some but not all studies have found a reduced NMDA binding affinity and expression in different brain regions of patients with MDD (for review, see [70]). Moreover, animal studies confirmed that dysfunctional subunits of the NMDA receptor may contribute to the pathophysiology of mood disorders, as mice lacking NR2A [71], NR2B in principal cortical neurons [72], or NR2D [73] NMDA receptor subunits exhibited strong anxiolytic- and antidepressant-like phenotypes relative to littermate control or heterozygous mice (Table **2**). Nevertheless, a recent study invalidated these observations for NR2D knockout (KO) mice, which displayed anhedonic- and depressive-like behaviors in the sucrose preference test (SPT) and TST [74] (Table **2**).

Overall, consistent with a promisingly significant role of NMDA receptors in mood disorders, a number of clinical trials demonstrated that targeting NMDA receptors with antagonists may be efficacious for treating mood disorders, as exemplified by the rapid and persistent antidepressant effect induced by ketamine, an NMDA receptor antagonist, following a single injection at sub-anesthetic doses in MDD or BP with or without treatment-resistance patients [75-79]. Clinical antidepressant efficacy of ketamine is clear, but studies in other psychiatric illnesses, like anxiety disorders, are more limited, although ketamine seems to persistently improve anxiety-like symptoms in anxious patients [80, 81], reduce PTSD symptom severity [82], or decrease OCD symptoms [83]. While ketamine given after a stressor did not protect against stress-induced depressive-like behavior for some preclinical studies [57, 84], it is an excellent candidate for plausible resilience-enhancing pharmaceuticals. Indeed, in mice, a single injection of ketamine (30 mg/kg) one week before an SD stress procedure protected mice against depressive-like behavior in the FST but did not prevent anxiety-like behavior in the EPM [57] (Table **2**). Furthermore, a single injection of ketamine (30 mg/kg) in mice 1 week before LH training protected against LH-induced coping deficits to deal with inescapable shocks [57] (Table **2**). In the CORT model, a single injection of ketamine (90 mg/kg) before a 3-week CORT treatment was protective against depressive-like behaviors in the splash test (ST) and the novelty suppressed feeding (NSF), but not against anxiety-like phenotype in the EPM [57] (Table **2**). Finally, in male Sprague Dawley rats, administration of ketamine (10 mg/kg), 2 weeks, 1 week, or 2 hours before inescapable tail shocks (IS) blocked the IS-induced decrease in time spent in social juvenile exploration at any of time intervals between ketamine and testing [85] (Table **2**). However, ketamine (30 mg/kg) buffered fear expression only when administered 1 week before contextual fear conditioning (CFC), but not 1 month, 24 hours, or 1 hour prior to CFC in 129S6/SvEvTac mice [86] (Table **2**). Interestingly, a single injection of ketamine 1 hour following a 3-shock reinstatement decreased subsequent fear expression but did not prevent fear reinstatement when administered 1 week prior to 1- or 3-shock reinstatement [86]. Together, these results suggest a long-lasting protective effect of ketamine prior to stressful events that persist up to 3 weeks, but that the timing of administering ketamine relative to a stressor is critical for its effectiveness.

8.2. The α-Amino-3-Hydroxy-5-Methyl-4-Isoxa-Zolepropionic Acid (AMPA) Receptors

In addition to NMDA receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors have also been proposed to be a major factor in the pathophysiology and treatment of mood disorders, but their role has been largely neglected. AMPA receptor activation is required for the antidepressant effects of ketamine, since blockage of AMPA receptor with NBQX antagonist pretreatment attenuated ketamine-induced antidepressant-like behavior in the FST [87]. Autoradiography in post-mortem brains of mood disorder-suffering subjects found increased AMPA binding density in the anterior cingulate cortex (ACC) of MDD patients [88] whereas GluR1 and GluR3 subunits of AMPA receptors were downregulated in the perihinal cortex of MDD and BP individuals [89]. In preclinical studies (summarized in [90]), acute or chronic stress exposure in animal models resulted in conflicting data concerning changes in AMPA receptor gene expression, depending on brain areas, especially for the GluR1 subunit. Numerous studies agree that the non-specific deletion of the GluR1-containing AMPA receptors in forebrain neurons reduced immobility in the FST and in the TST, increased time into the open arms in the EPM, and increased entries in the center in the OF as well as in the light compartment in the light dark test (LDT), suggesting that GluR1 deletion protects against acute stressors [91, 92] (Table **2**). However, others studies reported depressive-related behavior in GluR1 KO mice with true coping deficits in the LH paradigm, not caused by an altered pain sensitivity [93] (Table **2**). Thus, the protective effects of GluR1 deletion might only be due to exaggerated increases in locomotor activity during exposure to a novel environment

Table 2. Role of the different glutamatergic pathway-related key players in the stress-vulnerability and resilience in animals.

Species	Strain	Sex/Age	Model/Treatment	Stress	Duration	Results (*vs* Control)	Refs.
Mouse	C57BL/6J	♂ Adult	Vulnerable (↓ social avoidance vs non-stressed)	SD	10 days	GluR1 expression: ↑ in NAc GluR2 expression: ↓ in NAc	Vialou *et al*., 2010
			Resilient (no difference in social avoidance vs non-stressed)			GluR1 expression: no difference in NAc GluR2 expression: ↑ in NAc	
Mouse	mixed 129S1/Sv-p+Tyr+KitlSl−J/+; 129X1/SvJ	♂♀ 2-10 months	GluR1 KO (vs WT)	Ø	acute	EPM: ↑ entries in OA, ↓ times in CA LDT: ↑ entries in light FST: ↓ immobility	Fitzgerald *et al*., 2010
Mouse	B6N.129-Gria1tm2Rsp/J	♂♀ 15-30 weeks		Ø	acute	EPM/OF: ↑ time in OA/center FST/TST: ↓ immobility Social interaction: ↑ interaction	Maksimovic *et al*., 2014
Mouse	C57BL/6	♂ 3-6 months		Ø	acute	LH testing: ↑ latency to escape, ↑ escape failure	Chourbaji *et al*., 2008
Mouse	C57BL/6	♂ 12 weeks	GluR1 KO (glutamatergic neurons) (vs WT)	Ø	acute	EZM: no difference LH testing: no difference	Vogt *et al*., 2014
Mouse	C57BL/6N	♂ Adult	GluR1 KO 5-HT neurons) (vs WT)	Ø	acute	EZM/LDT: ↓ time/entries in OA/light FST/TST: no difference LH testing: no difference	Weber *et al*., 2015
Mouse	mixed C57BL/6J; 129Sv	♂ ND	GluR1 KO	Ø	acute	EPM: ↓ time in OA	Mead *et al*., 2006
Mouse	C57BL/6J	♂ Adult	Vulnerable (↓ social avoidance vs non-stressed)	SD	10 days	GluR2 expression: ↓ in NAc	Vialou *et al*., 2010
			Resilient (no difference in social avoidance vs non-stressed)			GluR2 expression: ↑ in NAc	
Mouse	CD1	♂ ND	GluR2 KO	Ø	acute	EPM: ↑ time in OA, ↓ entries in CA	Mead *et al*., 2006
Mouse	C57BL/6J	♂ Adult	mGluR2 KO	Ø	acute	EPM/B&W Alley/OF: no difference	De Filippis *et al*., 2015
Mouse	C57BL/6J	♂ 6 weeks	Vulnerable (↓ sucrose preference/↑ immobility in FST vs non-stressed)	CMS	28 days	mGluR2 expression: ↓ in PFC	Nasca *et al*., 2015
			Resilient (no difference in sucrose preference/immobility vs non-stressed)			mGluR2 expression: ↓ in PFC/hippocampus	
Mouse	ND	ND	mGluR2 KO			FST: ↑ immobility Coat-state: ↑ deterioration	
Mouse	mixed C57BL/6; 129Sv/Ev	♂ Adult	GluK2 KO (vs WT)	Ø	acute	EPM/OF:↑ time/entries in OA/center FST: ↓ immobility	Shaltiel *et al*., 2008
Mouse	C57BL/6J	♂ Adult	mGluR3 KO (vs WT)	Ø	acute	EPM/B&W Alley/OF: no difference	De Filippis *et al*., 2015
Mouse	mixed C57BL/6J; 129Sv	♂ Adult	GluK4 KO (vs WT)	Ø	acute	EZM: ↑ time/distance in OA Marble burying: ↓ marble NSF: ↓ latency to feed FST: ↓ immobility	Catches *et al*., 2012

(Table 2) contd….

Species	Strain	Sex/Age	Model/Treatment	Stress	Duration	Results (*vs* Control)	Refs.
Mouse	C57BL/6J	♂ 12-20 weeks	Vulnerable (↓ social avoidance vs non-stressed)	SD	12 days	mGluR5 expression: ↓ in NAc	Shin *et al*., 2015
			Resilient (no difference in social avoidance vs non-stressed)			mGluR5 expression: no difference in NAc	
			mGluR5 KO (vs WT)	LH	3 days	LH testing: ↑ latency to escape, ↑ escape failure FST/TST: ↑ immobility	
				SD	3 days	Social interaction: ↑ social avoidance	
				RS	3 days	SPT: ↓	
Mouse	C57BL/6J	♂ ND	mGluR5 KO (vs WT)	Ø	acute	FST: ↓ immobility	Li *et al*., 2006
Mouse	C57BL/6J	ND 10-14 weeks	mGluR7 KO (vs WT)	Ø	acute	FST/TST: ↓ immobility LDT: ↑ transitions EPM: ↑ time/entries in OA	Cryan *et al*., 2003
Mouse	mixed 129Sv; C57BL/6J; ICR	♂ 12 weeks	mGluR8 KO (vs WT)	Ø	acute	EPM: ↓ time/entries in OA	Linden *et al*., 2002
				RS	30 min	EPM: no difference	
Mouse	C57BL/6J	♂♀ > 10 weeks	NR2A KO (vs WT)	Ø	acute	EPM/LDT: ↑ time/entries in OA/light OF: ↑ time in center FST/TST: ↓ immobility	Boyce-Rustay & Holmes, 2006
Mouse	ND	♂ 50-70 days	NR2B KO (cortical neurons) (vs WT)	Ø	acute	EPM: ↑ time in OA FST/TST: ↓ immobility SPT: no difference	Miller *et al*., 2014
Mouse	C57BL/6J	ND 3 months	NR2D KO (vs WT)	Ø	acute	EPM: ↑ time/entries in OA LDT: ↑ time in light FST: ↓ immobility	Miyamoto *et al*., 2002
Mouse	ND	♂ Adult		Ø	acute	NSF/Marble burying: no difference TST: ↑ immobility SPT: ↓	Yamamoto *et al*., 2017
Mouse	129S6/SvEvTac	♂ 8-10 weeks	Ketamine (30 mg/kg) 1 week before stress	SD	2 weeks	EPM: did not reverse defeat-induced ↑ time in CA Social interaction: ↓ social avoidance FST: reverse defeat-induced ↑ immobility CFC/NSF: no difference	Brachman *et al*., 2016
			Ketamine (30 mg/kg) 1 week before stress			LH testing: ↓ latency to escape	
Mouse	C57BL/6NTac		Ketamine (90 mg/kg) 1 week before stress	CORT	3 weeks	EPM: did not reverse CORT-induced ↑ time in CA NSF/ST/FST: reverse CORT-induced ↑ latency to feed, ↑ grooming latency, ↑ immobility,	
Mouse	129S6/SvEvTac	♂ 8 weeks	Ketamine (30 mg/kg) 24 hours, 1 week, 1 month before stress	3-shock CFC		Fear extinction: ↓ freezing at 1 week Fear reinstatement: no difference	McGowan *et al*., 2017
Rat	Sprague Dawley	♂ ND	Ketamine (10 mg/kg) 2 hours, 1 week, 2 weeks before stress	IS		Social interaction: reverse IS-induced social avoidance at any of time	Amat *et al*., 2016
Mouse/Rat	NIH-Swiss mice Sprague–Dawley rats	♂ ND	LY392098 (0.5, 1 mg/kg) 1 hour before testing			FST: ↓ immobility	Li *et al*., 2001

Abbreviations: 5-HT: serotonin; B&W: black & white; CA: closed arms; CFC: contextual fear conditioning; CMS: chronic mild stress; CORT: corticosterone; EPM/EZM: elevated plus/zero maze; FST: forced swim test; IS: inescapable shock; KO: knock-out; LDT: light/dark test; LH: learned helplessness; ND: non-determined; NAc: nucleus accumbens; ND: non-determined; NSF: novelty suppressed feeding; OA: open arms; OF: open field; PFC: prefrontal cortex; RS: restraint stress; SD: social defeat; SPT: sucrose preference test; ST: splash test; TST: tail suspension test; WT: wild-type.

reported by all the studies. Interestingly, restricted ablation of GluR1 in glutamatergic neurons did not result in behavioral changes associated with mood disorders [94], whereas KO mice lacking GluR1 specifically in 5-HT neurons of the DRN, showed increased anxiety-like behavior [95] (Table **2**). This discrepancy between global and 5-HT DRN neuron-specific GluR1 KO might be related to a reduction in THP2 expression and activity in the DRN as well as reduction in tissue levels of 5-HT in GluR1 KO mice [95].

Hence, data concerning the association between the GluR1 subunit and stress resilience or vulnerability are not clear for now, but other subunits of AMPA receptors might be involved in protective action against adverse experience. For instance, mice resilient to a 10-day SD showed increased GluR2 mRNA expression compared to control mice, while susceptible mice displayed a decrease in GluR2 levels in the nucleus accumbens (NAc) [96] (Table **2**). Moreover, in adult male mice, overexpression of ΔFosB, a transcription factor targeting GluR2-containing AMPA receptors, specifically in the NAc reduced the propensity to develop social avoidance in mice subjected to chronic SD. Conversely, blockade of ΔFosB function promoted stress susceptibility [96]. Thus, induction of GluR2 in resilient mice appeared to reflect a direct effect of ΔFosB on the GluR2 gene, as ΔFosB binding to the GluR2 promoter is increased in these mice [96]. Yet, mice lacking the GluR2 subunit showed reduced anxiety in the EPM, but the markedly impaired motor competence of these mice precludes a definitive conclusion [97] (Table **2**).

Despite contradictory outcomes from GluR1 and GluR2 studies, AMPA potentiating agents might be a promising new approach for increasing stress resilience and preventing stress-induced depressive-like states. For example, AMPA potentiator agents administered 1 hour before an acute stressor (FST and TST paradigms) induced antidepressant-like effects in both rats and mice [98] (Table **2**). They also prevented against chronic stress-induced increases in corticosterone levels and stress-induced increases in latency to feed in NSF as compared with vehicle-treated mice [99]. Consequently, there is some evidence pointing to AMPA receptors as one potential molecular cause for individual stress vulnerability but also as a novel therapeutic targets for inducing resiliency for stress-related disorders.

8.3. The Kainate Receptors

Kainate receptors, a third glutamate ionotropic receptor, have also been implicated in anxiety and depression physiopathology, but still remain poorly explored. Among all the kainate receptor subunits (GluK1-5, previously called GluR5-7 and KA1-2), only the GluK5 subunit mRNA was decreased in the PFC of individuals with MDD or BP [100]. Also, decreased GluK2 mRNA expression in the entorhinal cortex has been found to correlate with MDD [89] as well as treatment-emergent suicidal ideation during treatment with escitalopram [101]. Moreover, genetic variations in the intronic region of the GluK2 gene suggested a potential association with somatic anxiety [102]. Further, a GluK3 gene polymorphism has been shown to be associated with recurrent MDD [103], while 2 single nucleotide polymorphisms (SNPs) in the GluK4 gene is associated with a protective effect against BP [104].

As previously mentioned, clinical evidences suggest that GluK2 may be a potential candidate gene in mood disorder susceptibility [89, 101]. Preclinical data are consistent with them because mice with genetically deleted GluK2 receptors exhibited less anxiety-like behavior in the OF and EPM and displayed an antidepressant-like phenotype in the FST, though these effects may be confounded by an increase of spontaneous locomotor activity [105] (Table **2**). Finally, GluK4 KO mice showed a reduction in anxiety-like behavior in the EZM, the marble-burying test, and the NSF paradigm, as well as an antidepressant-like phenotype in the FST and the SPT, without effects on locomotor activity [106] (Table **2**). In conclusion, progress remains to be made regarding involvement of kainate receptors in stress vulnerability or resiliency.

8.4. The Glutamatergic Metabotropic Receptors (mGluRs)

mGluRs are subclassified into three groups, based on sequence homology, G-protein coupling and ligand selectivity. In Group I, $mGluR_1$ is associated with schizophrenia, while $mGluR_5$ may play an important role in mood disorders [107]. In postmortem tissue, magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) studies found reduced $mGluR_5$ expression in MDD patients, whereas $mGluR_5$ binding was increased in OCD patients. Moreover, in Flinders Sensitive Line (FSL) rats, proposed to be a model of retarded depression, lower densities of $mGluR_5$ in the brain limbic structures were observed as compared to control Flinders Resistant Line (FRL) rats [108]. In two other models of anxiety and depression in male rats, elevated glucocorticoids and prenatal restraint stress, $mGluR_5$ protein expression was reduced in the hippocampus [109, 110]. Finally, segregation of chronically stressed mice into susceptible and resilient subpopulations showed that susceptible mice exhibited less $mGluR_5$ in the NAc than either resilient or control mice [111] (Table **2**). Moreover, after a 3-day exposure to LH, SD, or restraint stress, $mGluR_5$ KO mice exhibited enhanced susceptibility to stress-induced depression, social avoidance, and anhedonia [111] (Table **2**). However, both social avoidance and anhedonia in $mGluR_5$ KO was reversed by lentiviral rescue of $mGluR_5$ in the NAc [111]. Hence, $mGluR_5$-deficient mice failed to deploy effective defenses against chronic stress-induced depression, although Li and collaborators found a reduction of despair behavior in the FST [112] (Table **2**). Due to the outcomes variation, the role of $mGluR_5$ in stress resilience remains uncertain.

In Group II, clustering $mGluR_2$ and $mGluR_3$, the clinical data first suggested a strong increase in $mGluR_{2/3}$ level in the postmortem PFC of MDD subjects [113]. However, these data were later refuted by Muguruza's group which reported no changes in expression and density in the PFC of MDD subjects [114]. Based on the preclinical data, a decrease in $mGluR_{2/3}$ gene expression in the hippocampus and an increase in the frontal cortex was a hallmark of rats exhibiting depressive-like behavior [115, 116]. Indeed, vulnerable and

resilient mice to unpredictable chronic stress (UCMS) had a decreased hippocampal $mGluR_2$ expression, but only resilient mice exhibited 82% lower $mGluR_2$ expression within the PFC [117] (Table **2**). No consistent difference in anxiety-like behavior was found between mice lacking $mGluR_2$ and/or $mGluR_3$ and their respective controls [118] (Table **2**). Yet, $mGluR_2$ is essential for promoting resilience to stress, since $mGluR_2$ KO mice subjected to 28-day UCMS resulted in higher immobility in the FST, as well as a severe deterioration of the coat-state rating scale [117] (Table **2**).

In Group III, $mGluR_4$, $mGluR_6$, $mGluR_7$ and $mGluR_8$ have been suggested to be involved in mood disorder physiopathology. Due to the lack of specific ligands for these receptor subtypes, various studies have been conducted in genetically modified mice. Thus, $mGluR_7$ KO mice exhibited an antidepressant-like phenotype and anxiolytic-like behavior [119] (Table **2**). In contrast, naïve 12-week-old $mGluR_8$ KO mice displayed higher anxiety-related state in the EPM [120] (Table **2**). Interestingly, when $mGluR_8$ KO mice were tested in more stressful conditions or immediately after a 30-minute restraint stress in the EPM, no difference was observed between WT and KO mice, suggesting that the anxiety-like state of WT mice, but not KO mice, increases under more stressful conditions (Table **2**). In conclusion, Group III receptors might play a role in acute stress resilience, but their protective potential against chronic stress still need further consideration.

With the exception of the clear long-lasting protective effect of ketamine, many studies have reported discrepant results depending on the target glutamatergic receptors. However, it is clear that the glutamatergic pathway is involved in stress resilience, though further research is needed for understanding how it can modulate stress vulnerability or resiliency.

9. THE γ-AMINOBUTYRIC ACID (GABA) SYSTEM

GABAergic neurotransmission is currently considered a key player in the control of fear and anxiety, but the role of the glutamate-GABA balance is becoming increasingly relevant in the development and treatment of stress-induced mood disorders. Abnormalities in the benzodiazepine (BZD) site, localized on the $GABA_A$ receptor, have been associated with the etiology and modulation of anxiety from imaging studies (see, *e.g.*, the review of [121]). The GABAergic hypothesis in anxiety disorders has been well established, particularly in regards to successful efficacy of BZD in treating anxious patients. A recent meta-analysis of the existing MRS GABA studies across psychiatric disorders described lower GABA levels in MDD patients, but not in remitted MDD patients compared with healthy controls, and no significant difference in individuals with BP, panic disorder, or PTSD [122]. However, road traffic accident victims who developed PTSD had lower GABA-plasma levels 6 weeks after their accident. Interestingly, 75% of victims who had plasma GABA levels above 0.20 mmol/ml immediately after the accident and met criteria for PTSD 6 weeks after their accident were remitted at the 1-year follow-up, indicating that higher levels of GABA after a traumatic event may protect against chronic PTSD [123]. Seven-week CMS non-anhedonic rats developed a significant increase in cholecystokinin- and neuropeptide Y-positive GABAergic neurons density in the orbitofrontal cortex, as compared to anhedonic rats [124] (Table **3**). Thus, alterations in GABAergic transmission may represent some aspects of the pathophysiology of depression (reviewed in [125]).

9.1. The GABAergic Receptors

The development of more selective agents has led to the identification of two distinct classes of GABA receptors: $GABA_A$ and $GABA_B$. The pentameric $GABA_A$ receptor has been shown to have a critical role in the etiology of anxiety disorders, as patients with panic disorders or GAD show a reduction in BZD binding throughout the brain (for review, see [121]). A genetic association study revealed that common polymorphisms in the $GABA_A$ receptor α2, α3, α6, and γ2 genes do not play a major role in liability to anxiety disorders and MDD [126]. Feusner and collaborators reported an association between polymorphisms in the $GABA_A$ receptor ß3 subunit and higher symptom severity in anxiety and depression symptoms in a population of PTSD patients [127]. On the preclinical side, exposing juvenile rats to early postnatal stress resulted in an anxiety-like phenotype in adulthood associated with a decrease in the $GABA_A$ receptor α1/α2 ratio in both the amygdala and hippocampus, and α1/α3 ratio in the amygdala, suggesting that the α2 and α3 subunits might confer vulnerability to stress. As expected, specific deletion of the $GABA_A$ α1 subunit in corticotrophin-releasing hormone neuron enhance anxiety-like phenotype in the EPM and in the OF, impaired extinction of conditioned fear, but did not impact depressive-like behavior [128] (Table **3**). It is noteworthy that genetic inactivation of α2-containing $GABA_A$ receptors results in a depressive-like phenotype, as indicated by increased immobility in the FST and the TST and a trend for increased latency to feed in the NSF [129] (Table **3**). If $GABA_A$ α3 KO mice showed an enhance in swimming behavior, there is no evidence for an increase in the SPT [130] (Table **3**). However, α2 or α3 deletion, in global brain or in intra-hippocampal areas of adult mice, did not affect baseline anxiety-like behavior in the EPM or in the OF [130-132] (Table **3**). Finally**,** as homozygous $GABA_A$ γ2 KO is lethal in the perinatal period, heterozygous γ2 KO mice, with markedly attenuated expression of γ2 gene, was used to assess the protective role of this subunit in mood disorders. It appeared that $GABA_A$ γ2 plays a protective role, as γ2 KO mice had enhanced anxiety-related reactivity to natural aversive stimuli in the EPM and the LDT [133, 134] (Table **3**). Collectively, the findings on various KO mice $GABA_A$ receptors identify α1- and γ2-containing $GABA_A$ receptors as key subtypes mediating resilience against acute stressors, but the role of all subunits of $GABA_A$ receptors should also be studied in chronic stress conditions, with applications to the stressful life events in humans leading to mental disorders.

$GABA_B$ receptors are emerging therapeutic targets for treating stress-related disorders since deficits in cortical $GABA_B$ receptors has been observed in MDD and treatment resistant MDD (TRD) patients [135]. A recent study suggested that the $GABA_{B(1)}$ receptor subunit isoforms differentially regulate resilience or vulnerability to either early life

Table 3. Role of the different GABAergic pathway-related key players in the stress-vulnerability and resilience in animals.

	Species	Strain	Sex/Age	Model/Treatment	Stress	Duration	Results (*vs* Control)	Refs.
GABAergic neurons	Rat	Wistar rats	♂ 5–6 weeks	Resilient (< 10% within subject ↓ sucrose intake) (vs vulnerable)	CMS	7 weeks	CCK-positive GABAergic neurons: ↑ in ventral orbitofrontal cortex NPY-positive GABAergic neurons: ↑ in lateral orbitofrontal cortex	Varga *et al*., 2017
GABA(A) receptors	Mouse	mixed C57BL/6; FVB	ND	α1 KO (CRH neurons) (vs WT)	Ø	acute	EPM/OF: ↓ time in OA/center TST: no difference Fear extinction: ↑ freezing	Gafford *et al*., 2012
	Mouse	129×1/SvJ	♂ ND	α2 KO (vs WT)	Ø	acute	FST: ↑ immobility in first 2 minutes, no difference in last 4 minutes TST: ↑ immobility NSF: trend to increase latency	Vollenweider *et al*., 2011
			♀ ND				FST: ↑ immobility in first 2 minutes TST/NSF: no difference	
	Mouse	mixed C57BL/6J; 129X1/SvJ	♂ 12 weeks	α3 KO (vs WT)	Ø	acute	FST: ↓ immobility Sucrose preference: no difference	Fiorelli *et al*., 2008
	Mouse	mixed C57BL/6; 129/SvJ	ND	γ2 KO (vs WT)	Ø	acute	EPM/LDT: ↓ time/entries in OA/light CFC: no difference	Crestani *et al*., 1999
	Mouse	mixed C57BL/6J; 129S1/X1	ND Adult	γ2 KD (vs WT)	Ø	acute	EPM: ↓ time/entries in OA	Chandra *et al*., 2005
GABA(B) receptors	Mouse	BALB/c	♀♂ Adult	1A KO (vs WT)	Ø	acute	Sucrose preference: no difference FST: ↓ immobility TST: ↑ immobility Social interaction: ↓	O'Leary *et al*., 2014
					MS	14 days	Sucrose preference: ↓ FST: no difference TST: ↑ immobility EPM: no difference	
					SD	10 days	Social interaction/sucrose preference: ↓	
				1B KO (vs WT)	Ø	acute	Sucrose preference: no difference FST/TST: ↓ immobility Social interaction: no difference	
					MS	14 days	Sucrose preference: no difference FST/TST: ↓ immobility EPM: no difference	
					SD	10 days	Social interaction/sucrose preference: no difference	
GAT	Mouse	ND	♂ 6-8 weeks	GAT-1 KO (vs WT)	Ø	acute	OF/EZM: ↑ time/entries in center	Gong *et al*., 2015
	Mouse	C57BL/6J	♂ 12–18 weeks		Ø	acute	FST/TST: ↓ immobility EPM/LDT: ↑ time/entries in OA/ light	Liu *et al*., 2007
GAD	Mouse	mixed C57BL/6; CBA2	♂ Adult	GAD65 KO (vs WT)	Ø	acute	LDT: ↓ entries/distance in light FST: ↓ immobility	Stork *et al*., 2000
	Mouse	C57BL/6	♂ > 3 months		Ø	acute	OF/EZM: ↓ time in center/OA	Kash *et al*., 1999
	Mouse	C57BL/6	ND 8-12 weeks		Ø	acute	Fear extinction: ↑ freezing	Sangha *et al*., 2009

(Table 3) contd….

	Species	Strain	Sex/Age	Model/Treatment	Stress	Duration	Results (*vs* Control)	Refs.
GAD	Mouse	C57BL/6NTac	♂ 8-12 weeks	GAD65 haplodeficiency (vs WT)	Ø	acute	Generalized contextual fear and anxiety: no difference Pre-conditioning anxiety: no difference Depression-like behavior: no difference	Muller *et al.*, 2014
					juvenile stress	3 days	Generalized contextual fear and anxiety: no difference Pre-conditioning anxiety: ↑ emotionality score Depression-like behavior: no difference	
					isolation stress	for months	Generalized contextual fear and anxiety: ↑ emotionality score Pre-conditioning anxiety: no difference Depression-like behavior: no difference	
					JS + IS	ND	Generalized contextual fear and anxiety: ↑ emotionality score Pre-conditioning anxiety: no difference	
BZD	Rat	Wistar	♂ Adult	midazolam (1.5 mg/kg) 5 minutes before stress	RS	30 minutes	CFC: reverse stress-induced ↑ freezing	Maldonado *et al.*, 2011
				midazolam (1.0 µg in amygdala) 5 minutes before stress			CFC: reverse stress-induced ↑ freezing	
	Rat	Wistar	♂ ND	midazolam (0.25 mg/kg) 30 minutes before re-exposure to stress			Fear reinstatement: no difference in high-anxiety Fear reinstatement: ↓ re-conditioning freezing in low-anxiety	Skorzewska *et al.*, 2015

Abbreviations: BZD: benzodiazepine; CCK: cholecystokinin; CMS: chronic mild stress; CRH: corticotrophin-releasing hormone; EPM/EZM: elevated plus/zero maze; FST: forced swim test; GAD: glutamate decarboxylase; GAT: GABA transporter; IS: isolation stress; JS: juvenile variable stress; KD: knockdown; KO: knock-out; LDT: light/dark test; MS: maternal separation; ND: non-determined; NPY: neuropeptide Y; OA: open arms; OF: open field; RS: restraint stress; SD: social defeat; TST: tail suspension test; WT: wild-type.

maternal separation or 10-day SD stress [136]. Indeed, the authors reported that in the absence of chronic stress, $GABA_{B(1a)}$ KO and $GABA_{B(1b)}$ KO mice displayed antidepressant-like behavior in the FST, but no difference in the SPT [136] (Table **3**). Interestingly, following chronic SD, $GABA_{B(1a)}$ KO mice showed a decrease in social interaction and the SPT, while $GABA_{B(1b)}$ KO mice exhibited resilience as compared to WT stressed littermates (Table **3**). Similarly, after maternal separation, $GABA_{B(1a)}$ KO mice exhibited increased anhedonia in the SPT, whereas $GABA_{B(1b)}$ KO mice maintained the reduction of immobility in the FST (Table **3**). Anxiety levels in adulthood were unaffected either by genotype or chronic stress procedure in the EPM [136]. In conclusion, $GABA_{B(1a)}$ KO mice are more susceptible whereas $GABA_{B(1b)}$ KO mice are more resilient to both stress-induced anhedonia and psychosocial stress-induced social withdrawal.

9.2. The GABA Transporter (GAT)

The GABA transporter (GAT) also many play a major role in GABAergic transmission, as it participates in GABA homeostasis in the synaptic cleft. Because anxious and depressed individuals seem to have a deficit in inhibitory GABAergic activity, GAT may be involved in the pathogenesis of depression and anxiety. Nevertheless, there is little evidence concerning this hypothesis. A case-control association study found a link between two genetic variants located on the 5' region of the GAT-1 gene and severity of panic attacks in anxiety disorder patients [137]. Furthermore, individuals with an anxiety disorder display a positive clinical response to tiagabine, a selective GAT-1 inhibitor [138]. Preclinical studies in GAT-1 deficient mice support the role of GAT-1 in mood disorders, as they demonstrate an increase in resilience to acute stress in several behavioral paradigms related to antidepressant- and anxiolytic-like activity [139, 140] (Table **3**).

9.3. The Glutamic Acid Decarboxylase (GAD)

Another potential mechanism for the observed decrease in GABA levels in psychiatric disorders may involve abnormalities in the GABA synthesizing enzyme, glutamic acid decarboxylase (GAD) 65/67. Indeed, postmortem studies in patients with MDD revealed a significant reduction in GAD_{65} in the PFC [141] or in $GAD_{65/67}$ density in the hypothalamic paraventricular nucleus (PVN) [142]. Similarly, in both mice and rat models of depression, GAD_{67} expression was downregulated in the PFC [143, 144]. Preclinical data from mice lacking GAD_{65} confirmed the necessity of functional GAD_{65} for preventing anxiety-like behavior and fear generalization to neutral stimuli and resistance to fear extinction in the cued fear conditioning test [145-147] (Table **3**). But, surprisingly, deletion of the GAD_{65} gene elicited a reduction of stress-induced immobility associated with an enhancement of the swimming activity in the FST [145] (Table **3**).

Unlike homozygous GAD_{65} mutants, GAD_{65} haplodeficient ($GAD_{65}^{+/-}$) mice, which show a delayed postnatal increase in tissue GABA content in limbic and cortical brain areas, do not display an anxiety- or depressive-like phenotype, but rather exhibited similar emotionality to WT mice [148] (Table **3**). In order to investigate the importance of the GAD_{65}-mediated postnatal maturation of the GABA system in the development of PTSD, Muller and collaborators subjected $GAD_{65}^{+/-}$ mice to either juvenile variable stress, isolation stress, or a combination of both stressors before testing their adulthood emotionality in a behavioral test battery [148]. In generalized contextual fear and anxiety, stressed WT mice showed an increased emotionality score following all stress procedures, whereas $GAD_{65}^{+/-}$ mice were susceptible to isolation stress but resilient to variable stress [148] (Table **3**). In contrast, in pre-conditioning anxiety in the OF and EPM, $GAD_{65}^{+/-}$ mice were resilient to isolation stress but susceptible to variable stress [148] (Table **3**). Altogether, these data suggest that GAD_{65} haplodeficiency confers resilience to ELS-induced development of contextual fear generalization, which is commonly observed in PTSD patients.

9.4. Benzodiazepines in Promoting Stress Resilience

The fast anxiolytic effects of BZDs are well documented, and their use for prophylactic purposes have also been studied. Indeed, male Sprague-Dawley rats treated for 6 days with diazepam (5 mg/kg) and tested 1 hour after the last injection, displayed an attenuation of FST-induced enhancement of plasma corticosterone levels [149]. Similarly, pretreatment with midazolam (1.5 mg/kg), administered 5 minutes prior to a restraint stress, in male Wistar rats prevented stress-induced enhanced conditioned freezing response through activation of ERK1/2 pathway into basolateral amygdala [150] (Table **3**). Moreover, a single injection of midazolam (0.25 mg/kg) in low-anxiety but not in high-anxiety male rats 30 minutes prior to re-exposure to the CFC context reduced freezing levels and prevented fear reinstatement [151] (Table **3**). Thus, stimulation of the GABAergic pathway prior to stress exposure or re-exposure may be relevant pharmacotherapy in regards to PTSD prevention.

9.5. THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS (HPA)

The HPA axis is a key controller of endocrine and behavioral adaptation to stress by facilitating responses to threat. Perception of physically or psychologically stressful situations is followed by activation of the HPA axis, leading to a secretion of the neuropeptide corticotrophin-releasing hormone (CRH) from the PVN, which in turn activates the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary. Finally, ACTH stimulates the adrenal cortex, resulting in the secretion of glucocorticoids. Susceptible individuals exhibit persistently altered stress responses, acting principally upon a dysregulation of the negative feedback by endogenous glucocorticoids through the glucocorticoid receptors (GR), leading to chronic enhanced activity of the HPA axis and hypersecretion of glucocorticoids (for review, see [152, 153]). When glucocorticoids are hypersecreted over extended periods of time, the initially beneficial effects of HPA axis activation reverse into increased risk to develop a mood disorder. This may explain the increased pituitary and adrenal gland volume, as well as the elevated circulating levels of stress hormones, found in patients diagnosed with stress-related emotional disorders. These observations had even led to the development of the corticosterone (CORT) model in rodents, in which long-term exposure to exogenous glucocorticoids induced anxiety- and depressive-like phenotype, reversed by antidepressant administration [154]. Thus, effective therapeutics to improve stress resilience might be possible by targeting different levels of the HPA axis, such as CRH or GR.

9.6. The Corticotrophin-Releasing Hormone (CRH) and Its Receptors

Several studies have established that patients with mood disorders or PTSD present overactivity in CRH transmission. They contain higher CRH-positive neurons and CRH receptor density [152], though the contribution of CRH levels in the cerebrospinal fluid are still under investigation [155]. The preclinical data support this hypothesis, as adult mice susceptible to 10 consecutive days of SD showed increased CRH mRNA levels in the PVN, while no difference was reported in resilient mice [156] (Table **4**). Therefore, it is reasonable to expect that reduced CRH transmission may confer resilience to stress and protect against mood disorder development.

CRH predominantly acts through CRH_1 receptor to produce anxiety- and depressive-like symptoms; targeting the CRH_1 receptor might be relevant for preventing stress-related disorders. One study found that CRH_1-deficient mice spent a longer time in the light compartment in the LDT and in the open arms in the EPM as compared to WT mice [157] (Table **4**). Interestingly, leaving basal and stress-induced activation of the HPA axis intact after postnatal inactivation of CRH_1 receptor in mouse limbic structures, but not in the pituitary, induces an anxiolytic-like phenotype in the LDT and the EPM [158] (Table **4**). These data are consistent with the downregulation of CRH_1 receptors observed in the locus cœruleus (LC) and amygdala adult male Sprague-Dawley rats resilient to unpredictable and inescapable stress [159] (Table **4**). Thus, it is not surprising to observe an anxiolytic/antidepressant-like effect of CRH_1 receptor antagonism either in preclinical or in clinical studies (see, *e.g*., the review of [152]). In addition, a protective polymorphism formed by 3 SNPs located in intron 1 of the CRH_1 receptor, which either decreased sensitivity of the CRH_1 receptor or increased negative feed-back regulation of its functioning, was identified to lower effects of child abuse on adult depressive symptoms [160].

9.7. Cortisol and Its Receptors

A meta-analysis of 354 studies including 18,374 subjects across both depressed and control groups have reported greater cortisol levels in approximately two-thirds of depressed patients [155]. This observation was confirmed in an animal study in which adult male C57BL/6 mice were stratified into resilient or vulnerable subpopulations after a 10-day SD exposure [161]. Unlike control or resilient mice,

Table 4. Role of the different HPA axis-related key players in the stress-vulnerability and resilience in animals.

	Species	Strain	Sex/Age	Model/Treatment	Stress	Duration	Results (*vs* Control)	Refs.
CRH	Mouse	C57BL/6	♂ 8 weeks	Vulnerable (↑ social avoidance vs non-stressed)	SD	10 days	Crh mRNA levels: ↑ in PVN	Elliott *et al*., 2010
				Resilient (no difference in social avoidance vs non-stressed)			Crh mRNA levels: no difference in PVN	
CRH1	Rat	Sprague–Dawley	♂ Adult	Vulnerable (mean escape latency times > 2 SD vs non-stressed)	IS	2 hours	CRH1 expression: no difference in LC, amygdala, striatum CRH1 expression: ↓ in cortex	Taneja *et al*., 2011
				Resilient (escape latency times within 2 SD vs non-stressed)			CRH1 expression: ↓ in LC, amygdala, cortex CRH1 expression: no difference in striatum	
	Mouse	C57BL/6	♂♀ Adult	CRH1 KO (in pituitary)	Ø	acute	LDT: ↑ time in light EPM: ↑ time/entries in OA	Smith *et al*., 1998
	Mouse	mixed 129/Sv; C57BL/6	♂ 3-5 months	CRH1 KO (in anterior forebrain and limbic structures)	Ø	acute	LDT: ↑ time/entries in light EPM: ↑ entries in OA	Muller *et al*., 2003
CORT	Mouse	C57BL/6	♂ 8-12 weeks	Vulnerable (↑ social avoidance vs non-stressed)	SD	10 days	CORT level after DEX challenge: ↑	Jochems *et al*., 2015
				Resilient (no difference in social avoidance vs non-stressed)			CORT level after DEX challenge: no difference	
GR	Mouse	mixed C57BL/6; 129SV; CBA	ND 6 months	FBGRKO (forebrain-specific GR KO) (vs WT)	Ø	acute	FST/TST: ↓ immobility SPT: ↓	Boyle *et al*., 2005
	Mouse	mixed C57BL/6; FVB/N	♂ 3-6 months	GR-heterozygous KO (50% reduced GR gene)	Ø	acute	EZM/LDT/CFC: no difference FST: no difference CORT level after DEX challenge: ↑	Ridder *et al*., 2005
					LH	2 days	LH testing: ↑ latency to escape, ↑ escape failure	
					RS	30 min	CORT level: ↑	
				YGR (two-fold increased GR gene)	Ø	acute	EZM/LDT/CFC: no difference FST: no difference CORT level after DEX challenge: ↓	
					LH	2 days	LH testing: ↓ latency to escape, ↓ escape failure	
					RS	30 min	CORT level: ↓	
	Mouse	mixed 129/SvJ; C57BL/6	ND 17-22 months	FKBP5 KO (vs WT)	Ø	acute	EPM/LDT: no difference FST/TST: ↓ immobility	O'Leary *et al*., 2011
					RS	10 min	CORT level: ↓	
	Mouse	mixed 129/SvJ; C57BL/6	♂ 10-16 weeks	FKBP5 KO (vs WT)	Ø	acute	EPM/LDT/FST: no difference CORT level: no difference	Hartmann *et al*., 2012
					SD	21 days	EPM: no difference FST: ↑ swimming CORT level: ↓	

(Table 4) contd….

	Species	Strain	Sex/Age	Model/Treatment	Stress	Duration	Results (*vs* Control)	Refs.
GR	Mouse	C57BL/6	♂ 8-12 weeks	Vulnerable (interaction ratio < 100)	SD	10 days	CORT level after DEX challenge: ↑ Nuclear GR protein expression/GR-Hsp90 interaction: ↑ Hsp90 acetylation: ↓	Jochems *et al*., 2015
				Resilient (interaction ratio ≥ 100)			CORT level after DEX challenge: no difference Nuclear GR protein expression/GR-Hsp90 interaction/Hsp90 Acetylation: no difference	
				viral overexpression of acetyl-mimic Hsp90 mutant (in DRN) (vs WT)	SD	10 days	Social interaction: no difference	
	Mouse	129/Sv	♂ 3-12 months	HDAC6 KO	Ø	acute	OF: no difference EPM: ↑ time/entries in OA TST: ↓ immobility	Fukada *et al*., 2012
	Mouse	C57BL/6	♂ 8-12 weeks	$HDAC6^{Pet1Cre}$ KO (in 5-HT neurons)	Ø	acute	FST/TST: ↓ immobility	Espallergues *et al*., 2012
					SD	10 days	Social interaction: no difference	
MR	Mouse	C57BL/6J	♂ 3 months	MR overexpressing (vs WT)	Ø	acute	OF: ↑ time/entries in center LDT: ↓ latency to enter in light, ↑ entries in light CORT level (before and after stress): no difference	Lai *et al*., 2007
	Rat	Wistar	♂ 10 weeks	MR overexpressing (in BLA) (vs WT)	Ø	acute	EPM: ↑ entries in OA, ↑ time in OA (trend)	Mitra *et al*., 2009
					RS	2 hours	CORT level: ↓ EPM: ↑ entries in OA, ↑ time in OA (trend) OF: ↑ time in center	
Drugs	Mouse	129/Sv	♂ 3-12 months	NCT-14b (HDAC6 inhibitor)	Ø	acute	TST: ↓ immobility	Fukada *et al*., 2012
	Mouse	C57BL/6	♂ 8-12 weeks	ACY-738 (selective HDAC6 inhibitor, 5 mg/kg) 10 days before stress and 10 days throughout the stress	SD	10 days	Social interaction: reverse stress-induced ↑ social avoidance	Jochems *et al*., 2015

Abbreviations: 5-HT: serotonin; CORT: corticosterone; BLA: basolateral amygdala; CFC: contextual fear conditioning; CORT: corticosterone; CRH: corticotrophin-releasing hormone; DEX: dexamethasone; DRN: dorsal raphe nucleus; EPM/EZM: elevated plus/zero maze; FKBP5: FK506-binding protein 51; FST: forced swim test; GR: glucocorticoid receptor; HDAC: histone deacetylase; HPA: hypothalamic-pituitary-adrenal; Hsp90: heat shock protein; IS: inescapable stress; KO: knock-out; LC: locus cœruleus; LDT: light/dark test; LH: learned helplessness; MR: mineralocorticoid receptor; ND: non-determined; OA: open arms; OF: open field; PVN: paraventricular nucleus; RS: restraint stress; SD: social defeat; SPT: sucrose preference test; TST: tail suspension test; WT: wild-type.

vulnerable mice were characterized by plasma CORT non-suppression following the dexamethasone suppression test, a synthetic glucocorticoid which can be used to evaluate the function of the negative feedback control of the HPA axis [161] (Table **4**). Conversely, a meta-analysis of 17 studies reported lower cortisol levels in PTSD patients when compared to controls without previous exposure to trauma [162]. However, no difference was found between PTSD patients and resilient trauma-exposed controls [162]. The variable findings of glucocorticoid levels in MDD and PTSD subjects have posed challenges for understanding the role of the glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) in risk and resilience to the development of stress-related disorders.

GRs are expressed widely in the brain, principally in the PVN and hippocampus, and play a key role in stress-related homeostasis through an inhibitory feedback response. In absence of its ligand, GR is inactive and resides in the cytoplasm where it associates with the heat shock protein 90 (Hsp90) and its co-chaperone FK506-binding protein 51 (Fkbp5). This heterocomplex lowers the affinity for glucocorticoid affinity and reduces the efficiency of the nuclear translocation, but upon binding its ligand, the GR dissociates from its chaperone, becomes activated and translocates into

the nucleus for specific transcription. It appeared that some polymorphisms in the GR (Nr3c1) and Fkbp5 genes in combination with ELS strongly increases the risk of suffering from mood disorders in adulthood [163].

Clinical evidence suggests a reduced GR sensitivity to glucocorticoids in patients with depression, suggesting the impairment of GR-mediated negative feedback on the HPA axis [164]. Unlike the nuclear expression of GR, an increase in cytosolic GR protein expression in the PFC and the ventral hippocampus was observed in anhedonic adult Sprague-Dawley rats, induced by CMS [165]. This may be explained by the enhanced Fkbp5 protein expression [165], resulting in reduced function and translocation of GR to the nuclear compartment. Similarly, in a single prolonged stress model of PTSD, male Sprague-Dawley rats had a greater PFC and dorsal hippocampal GR levels than non-stressed animals but a decreased sensitivity to glucocorticoids [166]. Thereby, mice that underexpress functional GR may mimic patients with affective disorders, while in contrast, mice overexpressing GR may demonstrate stress resilience. In fact, forebrain-specific GR KO (FBGRKO) mice exhibited increased despair in the FST and the TST and increased anhedonia in the SPT [167] (Table **4**). The GR-heterozygous mice displayed normal behavior under basal conditions in a test battery for anxiety- and depression-like behavior, but exhibited coping deficits after a stressful challenge caused by the LH paradigm [168] (Table **4**). Moreover, these mice are non-suppressors in the dexamethasone suppression test or after a 30-minute restraint stress, suggesting that mice underexpressing GR have a predisposition for depression [168] (Table **4**). Conversely, mice carrying 2 additional copies of the GR gene are more resistant to developing helplessness [168] (Table **4**).

Because genome-wide association studies (GWAS) correlate variants in Fkbp5 to susceptibility to mood disorders [163], the emotional behavior of mice lacking this co-chaperone was assessed. Under basal conditions, ablation of Fkbp5 in young adult mice have no effect on emotional behavior, but after a 21-day SD paradigm, mice spent more time swimming in the FST [169] (Table **4**). Yet, aged Fkbp5-deficient mice (17-20 months old) exhibit an antidepressant-like phenotype [170] (Table **4**). Taken together, these data confirm that Fkbp5 is involved in stress vulnerability, since individuals with Fkbp5 deletion are less responsive to the adverse effects of acute or chronic stress.

Besides Fkbp5, the GR heterocomplex also needs Hsp90 for maintaining competent conformation for ligand binding. In a recent study, GR binding to Hsp90 was significantly elevated in SD vulnerable mice, coinciding with reduced Hsp90 acetylation and increased nuclear GR, while resilient mice did not show any difference compared to the control group [161] (Table **4**). Moreover, viral overexpression of a mutant protein mimicking the hyperacetylated state of Hsp90 was sufficient to promote resilient phenotype after SD [161] (Table **4**). Specifically, Hsp90 is under the control of the cytoplasmic histone deacetylases (HDACs). It is known that inhibition or depletion of HDAC6 leads to hyperacetylation of Hsp90, resulting in GR assembly impairment [171]. Consequently, targeting HDAC6 may be considered a novel key regulator of stress resilience. Under acute inescapable stressors condition, deletion of HDAC in the global brain or specifically in 5-HT neurons in male mice promotes an anxiolytic- and antidepressant-like phenotype [172, 173] (Table **4**). Interestingly, $HDAC6^{Pet1Cre}$ KO mice exposed to SD for 10 consecutive days failed to display the typical SD-induced increase in social avoidance [173] (Table **4**). It should be noted that acetylation of Hsp90 through pharmacological inhibition of HDAC6 may offer a possible method to mediate stress resilience in an at-risk population. Indeed, treating non-stressed mice with systemic injection of the HDAC6-selective inhibitor NCT-14b caused an antidepressant-like effect in the TST [172] (Table **4**). More interestingly, treating mice with a systemic injection of the selective HDAC6 inhibitor, ACY-738, 10 days prior to SD procedure, prevented the enhancement of SD-induced social avoidance [161] (Table **4**). In conclusion, preventative strategies targeting the GR heterocomplex may be quite effective, but to our knowledge, none of these molecules were clinically tested for MDD or anxiety disorders.

GRs and MRs operate in balance to coordinate stress-induced HPA axis activity. Compared to the GRs, the MRs hold a 10-fold higher affinity for cortisol and are predominantly expressed in limbic areas. Interestingly, dexamethasone-resistant depressed patients showed normal cortisol suppression by prednisolone, a glucocorticoid that binds to both the GR and the MR, suggesting a clear dissociation between GR and MR function in patients with depression [164]. Like GRs, there are numerous studies linking MRs with susceptibility for psychiatric disorders. Generally, MDD patients showed a decrease in MR mRNA expression in several brain regions (as reviewed in [174]). This is consistent with the findings of 3 independent studies, including data from a GWAS that looked at reduction of MR activity and correlated this with susceptibility to MDD, as well as hopelessness and rumination [175]. Conversely, women, but not men, carrying the functional MR haplotype 2, which is associated with higher MR activity, exhibited enhanced resilience to depression and displayed higher dispositional optimism and fewer thoughts of hopelessness [175]. Hence, men's susceptibility or resilience to depression does not seem to be modulated by the MR gene variability. This observation has led to the hypothesis that high MR levels confer resilience to stress-related psychopathologies. Indeed, genetic forebrain-specific MR-overexpression in mice present an anxiolytic-like phenotype [176] (Table **4**). More specifically, overexpression of MRs in the basolateral amygdala in adult male Wistar rats reduced restraint stress-induced corticosterone secretion 48h post-virus injection and reduced anxiety in non-stressed and restraint stress-exposed rats [177] (Table **4**). Such results have yet to be validated in the clinic, but recent data has shown that MR stimulation with fludrocortisone may improve cognitive deficits in depressed patients [178].

In conclusion, the data presented are strong evidence that the HPA axis through CRH, GRs, and MRs are important in mediating stress that may lead to mood disorders. Modulating these receptors using novel therapeutics may promote resilience to stressful events.

10. OTHER NEUROTRANSMITTER SYSTEMS

10.1. The Dopaminergic System

Insight into the biological variations in susceptibility and resilience can be gained by studying the mesolimbic dopaminergic system, particularly VTA dopamine (DA) neurons in the brain's reward circuit, which play a crucial role in mediating stress responses. Dysregulation of DA release or alterations in DA receptor expression has also been associated with depression, though some postmortem and imaging studies have provided conflicting results [179]. The Nestler laboratory supports the idea that resilience to chronic stress is mediated by diminished dopaminergic neurotransmission, as they showed that the VTA DA neuron firing rate was upregulated in SD susceptible mice, while there was no effect in SD resilient mice [180, 181]. But, reducing the firing rate of VTA DA neurons by overexpressing voltage-gated potassium (K^+) channels was sufficient to reverse susceptible mice into a resilient phenotype [180]. Likewise, phasic stimulation of the VTA DA neurons made SD-resilient mice susceptible [182]. Conversely, Tye and colleagues found that selective optogenetic inhibition of VTA DA neurons in non-stressed mice induced depressive-like behavior in the TST and the SPT [183]. However, phasic optogenetic stimulation of VTA DA neurons rescued unpredictable CMS-induced increase in immobility in the TST as well as the decrease in the SPT [183].

10.2. The Norepinephrine System

A large body of evidence points to deficiencies in brain norepinephrine (NE) neurotransmission as a key player in the pathogenesis of anxiety and depressive disorders. Specifically, an increase in NE neurotransmission through blockade of α2-adrenergic autoreceptor or NE transporter alleviates anxious and depression symptoms. Acute and chronic stress elicits dysregulation of the NE pathway, specifically through close interactions with the HPA axis and cortisol secretion. Thus, chronic traumatic stress leads to an hypoactivity of the NE system in brains of depressed subjects, resulting in decreased in NE turnover in limbic areas and increased α2-adrenergic binding sites in the LC [184].

NE neurotransmission also plays a key role in stress resilience. Ten days after SD, resilient mice exhibited increased NE levels in the VTA, but not in other limbic areas [185]. Interestingly, the susceptible phenotype of SD mice was reversed into a resilient phenotype after a 1-week daily treatment with a serotonin norepinephrine reuptake inhibitor (SNRI) or an α2-adrenergic receptor antagonist [185], suggesting that α2-adrenergic receptors might be a target of interest to increase stress resilience. Specifically, α2a-adrenergic receptors may play a potential stress-protective role whereas stress susceptibility might be mediated by α2c-adrenergic receptor. Mice lacking the α2a-adrenergic receptor exhibited more immobility in the FST and lower exploration of the light compartment in the LDT [186]. Target inactivation of the gene encoding the α2c-adrenergic receptor resulted in an antidepressant-like phenotype in the FST; conversely, overexpression of α2c-adrenergic receptor increased immobility in the FST [187]. Finally, the projection from the LC NE neurons to VTA DA neurons might be a critical factor in determining resilience to emotional stress. Chronic optogenetic stimulation of LC NE neurons projecting onto VTA stimulation reversed susceptible phenotype into a resilient one [185].

10.3. The Cholinergic System

The cholinergic system has also been implicated in mood disorder pathology. In medication-free subjects with recurrent MDD, a decrease in availability of the ß2 subunit-containing nicotinic acetylcholine (ACh) receptor (nAChR) throughout much of the brain structures has been observed, probably due to higher endogenous ACh levels rather than a decrease in the total number of receptors [188]. Secondly, blocking the muscarinic receptors with antagonists reduced depression and anxiety rating scale scores in patients suffering from recurrent MDD and BP [189]. Lastly, inhibiting acetylcholinesterase (AChE), an enzyme responsible for the breakdown of ACh, as well as hippocampal AChE knockdown (KD) in rodents had a depressive- and anxiety-like effect, which are reversed by administration of an AChR antagonist [190]. Taken together, these observations suggest that hyperactivity of the cholinergic pathway contributes to the pathophysiology of anxiety and depression. This hypothesis was supported in preclinical studies as KD or KO mice for the ß2 nAChR subunit exhibited anxiolytic- and antidepressant-like phenotypes [191, 192]. Similarly, mice lacking the ß4-containing nAChR displayed decreased anxiety-like behavior in the LDT and reduced fear memory retention in the cue-induced fear-conditioning task [193]. However, the results were variable when in depressive-like tests, as mice lacking the ß4 nAChR subunit showed increased immobility in the FST, but decreased immobility in the TST [193].

In addition to being involved in mood disorder states, the cholinergic system might also confer resilience to chronic stress. Unlike control animals, a 1-day SD stress induced an increase in social avoidance in hippocampal KD of AChE mice [190]. Moreover, downregulation of the ß2 subunit in the amygdala decreased social avoidance in mice subjected to a 3-day SD stress, suggesting that blockade of ß2 signaling in the amygdala increases resilience to social stress [192]. These data support the importance for maintaining ACh at homeostatic levels for promoting behavioral resilience to stress and preventing mood disorders.

As data on stress resiliency thus far demonstrate that there are a number of potential risk factors that increase susceptibility for developing mood disorders, particularly anxiety disorders, an emerging field of research is also focused on resilience in the context of aging.

11. RESILIENCE THROUGHOUT AGING

As an individual grows older, the risk for developing mood disorders, particularly anxiety disorders, increases with each passing year [5-7]. There is often high comorbidity of neuropsychiatric and neurodegenerative disorders, as well as of depression and anxiety disorders in elderly individuals [194-196]. Neuropsychiatric disorders in particular have been associated with accelerated cellular aging and neuro-

progression, as well as secondary medical illnesses such as cardiovascular disease, stroke, osteoporosis, dementia, diabetes, and metabolic syndrome [197-203]. The effects of stress throughout aging may contribute to heightened incidence of disease onset [204, 205]. The aging process may change biological processes (*i.e*. HPA axis function) that are essential to maintain resilience [206-209]; the breakdown of these systems could make a once-resilient individual susceptible, though the causality between symptoms and biological breakdown is still under speculation. Additionally, there may be risk factors during old age that contribute to this increased susceptibility to stress, such as neurodegenerative disorders and genetic factors such as telomere shortening associated with stress-related oxidative damage [196, 202, 205, 210, 211].

In order to combat this susceptible phenotype, it has been shown that increasing resiliency throughout the lifespan can slow the aging process, improve overall health, and protect against stressful situations in multiple species [212-214]. Importantly, several studies have discovered that adults aged 85 or older have a similar capacity for resilience as younger individuals [215-218]. However, it is equally likely that resilience is maintained in individuals throughout the lifespan, and that those with more susceptibility to disease are not included in this study due to earlier mortality. Despite this caveat, these studies have spurred an increased focus on developing behavioral interventions to attempt to improve resilience in older adults. Most research, however, is centered on developing measurement scales and identifying characteristics of resilience, and not many resilience interventions have been developed or thoroughly studied, especially for older adults [215]. Historically, resilience research has been largely centered on early childhood and adolescence, and has not been as widely studied in the adult or elderly population [219]. Only recently have researchers begun to study resilience in aging, and how the changes that occur in the body with age relate to the potential neurobiological underpinnings of stress resilience (reviewed in [220]). For instance, several groups have attempted pharmacologic approaches to increase the lifespan and improve resilience in pre-clinical models [211].

12. EFFECTS OF STRESS THROUGHOUT AGING

Previous work has shown that in a large sample of Canadians aged 18 and older, the perceived impact of stress exposure is strongest in older adults [221], suggesting that the level of observed stress correlates with the onset of stress-induced disorders [222]. It is generally accepted that the way that an individual ages is highly influenced by major life events and stressors (reviewed in [223]). Here, we will discuss the increased incidence of psychiatric disorders in older adults, and how mood disorders subsequently have a negative cyclical effect by accelerating aging.

12.1. Increased Incidence of Psychiatric Disorders in Older Adults

A literature review focused on World Health Organization (WHO) World Mental Health (WMH) surveys found that there was a proportional increase in projected lifetime risk versus prevalence with mood disorders. Additionally, estimates of projected lifetime risk of any DSM-IV mental disorder is increased throughout the lifespan [6]. It has been estimated that 25% of the population over 65, or 8.6 million people, contracts a mental disorder [224]. In particular, the overall rates of GAD are high (5-10% lifetime prevalence), but due to increased vulnerability in elderly people, late-life onset of GAD is as high as 25% [204, 225, 226]. Anxiety symptoms are common in older subjects, especially when they are medically ill, and depression and alcoholism are also often comorbid diagnoses [195]. Specifically, the prevalence of anxiety in community samples of older adults ranges from 15-52.3%, if sub-threshold anxiety symptoms are included as well [227]. Depressive symptoms are also prevalent in older adults, though some of the earlier literature reported values that varied from 1-23% depending on the population sampled [228]; however, a more recent review concluded that the prevalence of major depression is up to 16-42%, depending on whether the elderly were living in private households or in institutions [229]. Comorbid anxiety disorders and depression are common; one group found that as many as 35% of depressed patients aged 60 and older had at least one lifetime anxiety disorder diagnosis, and 23% had current diagnosis at the time of the study [230]. In younger individuals, the estimates range from 10 to 15% [231]. These studies, though varied, indicate that there is a general increased prevalence of psychiatric disorders with old age, and with it, an increased incidence of other mental disorders as well as secondary illnesses.

One specific group that experiences increased risk for a psychiatric disease throughout life is the veteran population. Several studies have recently shown that elderly individuals experience greater levels of stress after war, and respond differently to social support aimed to improve mental health [232, 233]. For instance, one study, which assessed individuals along the Lebanese border after the Second Lebanon War, found that the elderly reported significantly higher levels of stress symptoms, and lower levels of posttraumatic recovery as compared with younger age groups [232]. Additionally, older veterans experience PTSD at higher rates than younger veterans; in other words, the longer the time from the experience of war, the more likely an individual is to begin experiencing symptoms of PTSD, possibly due to the phenomenon of delayed-onset PTSD. One study found that approximately 1 in 10 US veterans experiences a clinically significant exacerbation of PTSD symptoms in late life, at an average of nearly 3 decades after their worst trauma [234]. Though the mechanisms of this late-life exacerbation were not discussed, it is possible that the aging process contributed to this intensification of trauma-related stress reactivity leading to PTSD.

In terms of factors that may contribute to the exacerbation of PTSD in older US veterans, a recent study was published that assessed loneliness [235]. The authors found that loneliness is prevalent among older veterans in the US, as 44% reported feeling lonely at least some of the time, with 10.4% reporting that they often felt lonely. The authors correlated increased age, trauma, perceived stress, and several other factors with the severity of loneliness and concluded that interventions might aid in mitigating loneliness, through social support and the eventual reduction of depressive

symptoms. However, no specific interventions were suggested or outlined in the study. Another study echoed these effects and found that a significant portion of older male veterans in the US contemplates suicide, with a higher rate of suicidal ideation among combat veterans as compared with non-combat veterans [236]. Both studies conclude by suggesting interventions that improve social connectedness to decrease loneliness, though no specific interventions were proposed.

These data are in stark contrast to a study that assessed older veterans and found that 69.5% of US veterans aged 60 and older were considered resilient, which they characterized as a high number of lifetime traumas and low current psychological distress [237]. These individuals were highly likely to have been college or higher level educated, and had high levels of emotional stability, social connectedness, and positive perceptions of the military's effect on one's life. Whether these characteristics existed before the experience of these traumas, or were built as a result of them, is unknown, but it is interesting to consider the possibility that these veterans had with high levels of resilience to begin with, and despite their experiences with multiple lifetime traumas, came away without disease. It is also possible that the generation of the cohort may have an impact on the outcome; specifically, the older generation in this cohort may be more resilient in general than the younger generation, though to our knowledge, no studies have informed on generational differences in regards to stress resilience. According to the APA's Stress in America survey from 2011, 23% of Baby Boomers, or those born between 1946 and 1964, reported decreased stress levels, and this may be because they were more likely to have grown up in two-parent households, with safe schools, job-security, and post-war prosperity; they also report decreased stress levels [238]. Thus, it is possible that there may exist a generational difference for stress resilience, and that this is manifested in the US veteran study, though no studies have directly tested this hypothesis.

12.2. The Role of Mood Disorders and Stress on Accelerated Aging

Experiencing chronic stress is a large risk factor for developing mood disorders, and both stress and mental illness may contribute to accelerated aging. It was shown that chronic psychological stress in rats affect genes that are critical for longevity [239]. Stress has been found to impact the developmental process, especially during critical developmental stages [240]. In general, however, there are complex interactions between stress and aging, as one can promote the other [241]. It has been shown that the peroxisome proliferator-activated receptor γ (PPARγ) may be a critical mechanistic link between aging and stress [241]. For example, PTSD has been associated with elevated risk for age-related diseases; it has been hypothesized that chronic PTSD is a form of persistent life stress that elevates oxidative stress and leads to accelerated cellular aging [202]. Elevated rates of aging-related biological and functional decline, specifically through accelerated cerebral white matter aging, was also found in patients with schizophrenia and MDD [203]. Stress experiences, therefore, appear to be interlinked with aging processes and psychiatric disorders, and the combination of the two may have large consequences on the rate of aging.

13. BENEFITS OF STRESS RESILIENCE IN AGED ADULTS

Though the risk of contracting mood disorders and other diseases increases with age, there are individuals who are able to avoid these risks, and succeed in living healthily throughout the lifespan. Thus, strategies that enhance resilience may slow aging [242]. Here, we will discuss how resiliency not only improves general well-being, but also how it may function to slow the process of aging.

13.1. Stress Resilience and Improved Health in Aged Adults

Having components of stress resiliency has been correlated with high functioning and successful aging in older adults. One group demonstrated that several markers of resiliency in persons older than 85 years include intact cognitive function, high mobility, and good nutritional status, and that these traits improved the likelihood of recovery from disease, and in performing activities of daily living (ADLs) [243]. Another group attempted to estimate the likelihood of and the factors associated with recovery from exhaustion in older adults, which is a common ailment for this population. They found that among individuals aged 69 or older, resiliency was associated with physical and psychological well-being in the face of persistent exhaustion [244].

13.2. Stress Resilience and Slowed Aging

In fact, as an individual grows older, stress resilience becomes increasingly important to continue to age successfully. Several studies have demonstrated that the older individuals are, the more resilience becomes a critical factor in maintaining health and longevity, and the more that adults self-rate as successfully aging [214]. For instance, one group studied centenarians, nonagenarians, and octogenarians, and found that nonagenarians aged 94-98 with increased resilience had a 43.1% higher likelihood of living to be 100, or becoming a centenarian, than those with lower resilience [245]. This suggests that the impact resilience becomes more pronounced at older ages, and greatly contributes to healthy lifespan.

In one review, the resilience framework was applied in two case studies of resilience among patients with Alzheimer disease (AD), and found that individuals with dementia may still lead meaningful lives, and that the resilience process may contribute to a more positive dementia experience [246]. The key point of this review is that the field of gerontology should be striving not for successful aging, but for resilience, which has a fundamental role in aging. Importantly, improving resilience and improving longevity is possible for all adults regardless of social and cultural background, or physical and cognitive impairments [246].

14. CHANGES THROUGHOUT AGING THAT SHIFT A RESILIENT PHENOTYPE INTO A SUSCEPTIBLE ONE

Though it is evident that increased resilience is beneficial throughout life, it is possible for an individual to gradually

lose a resilient phenotype as a result of the aging process. There are several mechanisms that are critical for maintaining resilience that are vulnerable to wearing down and making a once-resilient individual susceptible to stressors and the development of mood disorders. These include HPA axis dysfunction, brain atrophy in regions that are most actively protective against stress, genetic causes, loss of coping abilities, and the onset of a neurodegenerative disorders. Additionally, early-life or critical-period stressors are factors that may accelerate the resilient mechanism breakdown.

14.1. HPA AXIS Dysfunction in Aging

As discussed previously in this review, the HPA axis modulates stress responses by facilitating responses to threat, and susceptible individuals exhibit persistently altered stress responses characterized by enhanced activity of the HPA axis and secretion of glucocorticoids [152, 153]. Importantly, the HPA axis may be perturbed by exposure to prolonged stress that leads to deleterious effects, and HPA axis dysfunction has been correlated with age-related diseases such as depression and cognitive disorders [208] and this predisposes individuals to deleterious effects such as unstable emotional regulation [209]. For example, there could be either decreased aldosterone, or hyperaldosteronism resulting from increased ACTH stimulation that occurs with age [206, 208]. Cortisol may also be increased with aging, though the evidence supporting this claim is not conclusive [209]. To date, there are few studies that assess specific changes in the HPA axis that occur throughout aging that may contribute to mood disorder onset, and much work needs to be done to elucidate the what contributes to HPA axis breakdown, and how this may be prevented.

14.2. Telomere Shortening and Genetic Factors Associated with Mood Disorder Onset

In addition to changes brain morphology and stress axis functioning, there are also genetic markers that may either predispose individuals to developing mood disorders, or epigenetic changes that induce a susceptible phenotype. A large body of research has been dedicated to investigating the relationship between telomere length and health [247, 248]. Reduced telomere length has been associated with a number of chronic somatic diseases normally associated with aging but also implicated in psychiatric diseases such as depression [249-251]. Despite the established role of telomere length in health and aging, there are only a few therapies have been developed to combat the telomere shortening process. For instance, there have been several small stress reduction and wellness studies that have examined the potential to elongate telomeres *in vivo* over short periods of time [252]. The recent interest in gene therapy has led to the development of telomere-enhancing drugs not only as a cancer therapy [253], but also as a method to potentially slow the aging process, as a recent biotechnical company BioViva, based in Texas, has proposed.

In regards to genetic markers and polymorphisms that may indicate resilience, if 5-HTTLPR short (s)-allele carriers have reduced resilience to stress in young adults, in older adults, it appeared that though the s allele had less of a direct effect on resilience, it did correlate with poorer self-rated successful aging, as well as cognitive performance, suggesting that carrying this gene throughout life has an impact on quality of life in old age [254]. A separate study found that SNPs in the FK506 binding protein 5 (FKBP51) gene is an indicator of increased risk to develop PTSD and MDD when exposed to traumatic events [255]. The trauma can induce changes in FKBP51 protein expression and impair glucocorticoid signaling [255].

Epigenetic changes throughout the lifespan may also greatly contribute to disease susceptibility, and are more commonly studied than single genes, as both aging and stress are associated with changes to the epigenome [256-258]. Indeed, DNA methylation changes are associated with an aging clock, which has been implicated as a biomarker of aging [259]. In general, aging has been known to affect specific regulatory gene elements such as enhancers, promoters, and CpG islands [260]. It was found that in mice, age-associated hypomethylation was enriched at super-enhancers at highly expressed genes that are critical for liver function, and hypermethylation was enriched at CpG islands. These changes were suppressed in calorie-restricted mice and in mice treated with rapamycin (two possible therapies discussed later in this review) [260]. Epigenetic changes as a result of stress may also occur at the level of microRNAs (miRNAs). For instance, the Nestler laboratory found that β-catenin mediates pro-resilient and anxiolytic effects in the NAc of mice, which affects miRNA regulation through Dicer1, which is important in maintaining stress resilience [261]. These studies suggest that lifestyle changes may confer epigenetic modifications that contribute to longevity. Overall, it seems that several genetic changes, either inherited or changed over time by telomere shortening, genetic polymorphisms, or epigenetic modifications, may contribute to age-related disease onset.

14.3. Correlation Between Age-Related Cognitive Decline and Mood Disorders

With the onset of a neurodegenerative disorders or age-related cognitive decline, the risk for developing a mood disorder increases, and *vice versa* [262-265]. Shimada and colleagues found that older adults with depressive symptoms have increased risk of cognitive impairment and dementia, particularly AD and vascular dementia [263, 266]. Additionally, anxiety is a common symptom among patients with a cognitive impairment [5]. In cases such as these, the mood disorders correlate with poorer outcomes in patients, and the two disorders often worsen in tandem [5]. It is possible that these cognitive impairments linked to these mood disorders are induced by cellular loss that occurs with age. In the aging brain, it is common to observe atrophy of various regions due to cell loss and tract-specific white matter degeneration [267, 268]. Although brain atrophy in aging has mostly been studied in AD and other cognitive disorders, there are several studies that indicate that depressive symptoms and other mood disorders are associated with changes in both gray and white matter, including atrophy [269]. White matter lesions are frequently found in patients with late-life depression, which is a characteristic that overlaps with dementia [269].

The hippocampus undergoes several structural changes both grossly and at the cellular level with aging, and these have been correlated with cognitive decline in both animals and humans [270]. Although similar hippocampal alterations occur both with normal and pathological aging, in the case of neuropathologies these changes are exacerbated (increase in inflammation and decrease in trophic factors, decreased histone acetylation) [270]. Smaller hippocampal volume has been also associated with depressive symptoms, as well as stress and anxiety [271-273]. The PFC and the amygdala also undergo a plethora of changes during aging [274]. The modulation of stress responses during aging could be affected by changes in PFC-basolateral nucleus of the amygdala. Thus, insensitivity of the PFC-basolateral amygdala pathway to stress could constitute a mark of health, while the alteration of this specific pathway could be involved in mood disorders [274].

Overall, changes in brain region integrity may have effects on brain network function, and specifically the default mood network, cognitive control network, affective/ frontolimbic network, and corticostriatal circuits, which may be directly relevant for mood disorder onset (reviewed in [275]).

14.4. Critical Period Stressors Contribute to Resilience Mechanism Breakdown

The breakdown of brain functions necessary to maintain resilience could likely be induced not just by age, but by an ELS that has long-term deleterious effects. Exposure to stress during critical periods, such as during childhood, adolescence, and early adulthood, may cause an individual to become even more susceptible to stress in the future, and can lead to disease and a number of neuropsychiatric diseases [242, 276, 277]. Specifically, adverse childhood experiences (ACEs), including physical, sexual, and emotional abuse, have been correlated with depression in older adults [277]. The number and types of childhood maltreatment also affect the risk of depression, as cumulative stress has a negative effect on likelihood for mood disorders [242]. It has been shown that several significant important predictors of lifetime history of MDD included non-verbal emotional abuse in males, and peer emotional abuse in females at 14 years of age [242]. For PTSD, the critical periods of vulnerability to ACEs have been found to be the pre-school (age 4-5) and pre-adolescent (age 8-9) periods, and that the type and timing of ACEs affect severity of symptoms [278].

Though little is known about the underlying biology of this effect of early childhood trauma on late-life disorders, it has been noted that early childhood adversity such as abuse, neglect, or exposure to violence increases pro-inflammatory responses [279], affects patterns of gene expression regulated by inflammatory signaling [280], and quickens the process of telomere shortening [249] (as described earlier in regards to stress vulnerability and accelerated aging). One study found that children exposed to maltreatment had smaller volumes of the PFC and the hippocampus, greater activation of the HPA axis, and changes in inflammation levels as adults [279]. Another study found that stressors induce persistent changes in the HPA axis and affect its ability to respond effectively to stress in adulthood [281]. It has also been shown that telomere length may be associated with severity of ELS [249, 282]. 5-HT has been suggested to play a critical role in the maturation of brain systems that modulate emotional functioning in adults [283]. Specifically, inactivation of 5-HT receptors during development produce behavioral abnormalities related to neuropsychiatric diseases such as anxiety and depression [283, 284]. 5-HT has a suggested role in resilience, as previously discussed in this review, and may represent an essential target system that is most sensitive during developmental periods and may induce later-life psychopathology. Overall, the effects of stress during early, vulnerable periods in life may confer long-lasting biological changes to processes necessary to maintain resilience such as nervous, endocrine, immune, and genetic systems; these changes affect an individual's response to future stressors, and lead to faster aging and disease.

15. SEX DIFFERENCES IN AGING AND STRESS RESILIENCE

When considering factors that may contribute to stress susceptibility in old age, it is important to note the role that gender plays in regards to aging and in responding to stressful experiences.

15.1. Sex Differences in Aging

Several studies have attempted to assess sex differences in the aging process, and have discovered a number of characteristics that distinguish between male and female longevity. Women appear to live longer than men, as the average life expectancy for women is 83.5 years, and for men, 79.5 years [285]. This increased lifespan of women may be due to the rate at which telomeres shorten in males and females, though there has yet to be a study that directly links sex, telomeres, and lifespan observed across multiple species [286]. Another hypothesis links responsivity of the immune system to longevity and susceptibility, though the studies assessing this hypothesis are small and not conclusive [285]. A recent study used resting-state networks to study sex differences in normal age trajectory, and found that males and females both showed decreases in connectivity with age, but at different rates, which may explain the rates of aging [287]. Yet, paradoxically, despite living longer lives, women generally experience worse health throughout life than men [285, 288]. This decreased quality of health throughout life is likely due to an increased vulnerability to stress in women, as women seem to be more susceptible to stress than men throughout the lifespan [289].

15.2. Differential Sex Effects of Stress Throughout the Lifespan

Sex differences in stress responses are found at all ages, and are related to gonadal hormone changes that occur throughout development and maturation, and sex chromosome genes (reviewed in [290]). In general, females are twice as likely to develop anxiety disorders such as PTSD than males [233], even though some studies suggest that the probability of trauma exposure in females is lower [291]. Older depressed females were observed to have higher GR immunoreactivity in postmortem hippocampal tissue than

elderly depressed males [292]. Women also seem to lose hippocampal volume more rapidly than men in older age, according to one study, which used cerebral magnetic resonance imaging (MRI) [271]. There also seems to be indication that epigenetic mechanisms may promote sexual dimorphism in the brain in regions such as the hypothalamus due to sex hormone exposure during development [293]. This differentiation may create susceptibilities between males and females for psychiatric disorders. Yet, despite some hints about how females seem more likely to develop mood disorders, the exact neurobiological underpinnings of this increased susceptibility are not well known, though several studies have provided insight into potential mechanisms. It has been hypothesized that prepubertal stress induces long-lasting changes in brain regions such as the hippocampus and that these effects are sex-specific [276]. Specifically, one study found there prepubertal stress impaired hippocampus-dependent behavior in males (CFC), yet enhanced hippocampus-dependent behavior in females (spatial navigation and memory retention), suggesting differential sex effects of brief, variable stress during the prepubertal phase.

15.3. Peri- and Post-menopausal Periods as Windows of Vulnerability for Women

Recent research has attempted to describe female's heightened response to stressors by exploring the effects of stress during peri- and post-menopausal periods, as these represent windows of vulnerability for women to develop mood disorders [294-298]. Specifically, women are 2 to 3 times more likely to experience a first episode of depression during the peri-menopausal period [299, 300].

A reason for this increased susceptibility to stress could be due to the loss of gonadal hormones in females and their metabolites that are critical for stress regulation [290]. Ovarian estradiol secretion ceases at menopause and is followed by low levels of circulating estradiol [301]. Interestingly, one study found that age after menopause impacted the effect of estradiol hormone replacement therapy on mood after a psychosocial stress situation. This is important in light of previous studies, which demonstrated that estradiol improves mood in women in the menopause transition, but not older post-menopausal women. Thus, estradiol administration may be modulating emotional reactivity to stress by sensitizing older women to its adverse effects [302]. Though a specific mechanism is not addressed in this study, it suggests that estrogen receptor function shifts during the post-menopausal phase in women, and that this shift may be critical in mediating women's responses to stress. Several other groups have demonstrated the effects of estrogen receptor function shifts by examining mood in pre- and post-menopausal women, in which estradiol treatment has differential effects in both populations [302-304]. Indeed, in line with these studies, it has been suggested that the rapid decline of gonadal hormones, as well as ovarian senescence, in women and the cellular aging process promotes stress dysregulation in women [290, 305]. Thus, females are at greater risk for mood disorders induced by stress throughout life, and this should be considered when developing preclinical models or stress resilience enhancers that would benefit both males and females. It is possible that the male and female populations may require separate therapeutic strategies based on the differences in their stress reactivity, as well as the significant influence of hormonal states.

16. BEHAVIORAL STRATEGIES OF PREVENTING MOOD DISORDERS EXACERBATED WITH AGE

As there currently exists no pharmaceutical therapies for prevention of mood disorders in old age, one option is to implement behavioral strategies to prevent mood disorders in aged adults. Though very few intervention programs exist for elderly adults, there are several intervention programs that have been developed to increase resilience for the general population.

16.1. Intervention Programs

One example of an intervention program aimed to increase resilience is the American Psychological Association (APA)'s Road to Resilience program, which sought to promote resilience in in middle and high school students affected by the 9/11 terrorist attacks through focus groups in several major cities [306]. There are plans to provide psychologist-led workshops, forums, and lectures, but this program is not validated in older adults [306]. Meditation and Physical (MAP) training was also implemented in a small cohort of young mothers who were recently homeless and suffered from physical and sexual abuse, addiction, and depression. After 8 weeks, measures of aerobic fitness increased, and symptoms of depression and anxiety decreased [307]. However, though these positive preliminary results are promising for developing more refined and effective interventions, it is important to note that these examples have been published as pilot studies, and that none of them have extensive or long-term evaluation of their impact on resilience, or very large sample sizes in their original studies (for review, see [215]).

For current active duty military members, there exists the US Army Ready and Resilient Campaign (R2C) is one that attempts to build resilience in soldiers, army civilians, and their families, and the Army spends about $50 million a year on this program alone. In 2013, there existed over 94 different prevention or resilience programs within the Department of Defense (DoD). As opposed to the aforementioned studies, the impact on resilience from these programs has been evaluated, but no consistent, significant impact has been uncovered yet [308]. Thus, overall, resilience behavioral training is in its infancy and there exists a dearth of evidence validating that these behavioral programs are actually effective [309].

The only intervention programs in existence for older adults are implemented primarily after the onset of symptoms. For instance, though the exact causes of increased depression in aging is unknown, some research suggests that deficits in biological rhythmicity can contribute to onset of depressive symptoms. One option for these patients is using bright light therapy (BLT), in which bright blue light is shone daily in elderly patients' homes. In essence, the patients are to sit in front of a light box for 60 minutes each day for the duration of the study, during the middle of the day [310]. One group found that 3 weeks of BLT treatment

caused a reduction in MDD symptoms, including mood, sleep and cortisol hyperexcretion [311]. There also exist elderly suicide prevention programs, which consist of community workshops, interpersonal psychotherapy, and individual counseling. One review summarized 19 studies that assessed suicide prevention programs for adults aged 60 or older, and found that most studies observed a reduction in the level of suicide ideation or suicide rate of their respective communities [312]. The authors point out, however, that none of the studies aimed to improve protective factors.

Despite these small studies, building resilience through behavioral interventions in older adults is a field that requires much more investigation. Most research concludes with suggestions rather than definitive evaluations; for instance, savoring positive experiences was examined in older adults, and the authors reached the conclusion that positive psychological interventions to enhance resilience would be beneficial [313]. In general, positive emotions correlates strongly with resilience and well-being, and these could be the foundation for building effective resilience programs, or happiness interventions, for both the general population and the elderly [222, 313-315]. However, to our knowledge, no specific interventions have been established. Thus, the field of resilience enhancement in the elderly can potentially gain insight from resilience studies on other populations such as children and adolescents, but would likely find more value in studies that have examined resilience among specific groups of older adults, such as veterans or groups that come from specific backgrounds or experienced similar adversities. Because resilience is such a dynamic process, one suggestion has been to develop individualized resilience enhancement programs for older adults [215, 316, 317].

16.2. Exercise Therapies and Caloric Restriction (CR)

A popular intervention is regular exercise or high mobility, as a number of studies have correlated regular exercise and physical strength with higher emotional resilience in adults [18, 318, 319], and contributes to successful aging [320-323]. In addition to its effectiveness in preventing or alleviating heart disease [324], exercise has also been shown to improve mental health in older populations [325]. Increasing interest has been focused on using exercise to promote healthy aging and as a treatment for older people with and without psychiatric illnesses [326]. In regards to resilience, in a study of participants 72 years or older, it was demonstrated that high mobility was a positive predictor and a marker of resiliency in this population [243]. In general, the molecular processes of exercise are ones that attenuate typical signs of aging, such as inflammatory processes and telomere length [327, 328]. Additionally, since maximal oxygen capacity decreases with age, due to decreases in aging skeletal muscles, exercise can have a restoring effect on health; it also has effects in neurodegenerative diseases and oxidative stress regulation, even in frail elderly [327]. These studies collectively suggest that exercise has a multitude of benefits, but importantly, they may increase health and resilience in elderly populations.

In line with exercise therapies, weight management over time has also been correlated with resilience, particularly in the older population [329]. Thus, caloric restriction (CR) has been used as a therapy to postpone the detrimental aspects of aging, and is defined as a decrease of 30% to 60% *ad libitum* feeding without malnutrition (reviewed in [211, 329]). It has been shown to be effective in improving resilience, but that the effects of exercise have proven more consistently beneficial [248]. Numerous studies since 1935 have shown that lifelong CR increases mean and maximum lifespan and delays age-associated disease in several species, including mice, rats, and rhesus monkeys [330-332]. For instance, some studies have found that some dietary regimes and over a dozen single-gene mutations can extend the mean and maximal lifespan in mice [333, 334]. It has been suggested that CR may suppress inflammatory cytokines, a common risk factor for a number of chronic diseases [335]. Though CR is not used primarily as a method to alleviate mood disorders, it has been shown to improve mood states such as depression, but to our knowledge, the relationship between CR and mood has only been examined in aged men [336, 337]. Altogether, these studies provide evidence that therapeutic interventions in older adults would benefit from incorporating exercise and CR in their programs, though some groups are working to achieve the effects of these therapies, as not all individuals can withstand the rigor of these approaches.

17. POTENTIAL METHODS TO TARGET NEUROBIOLOGICAL SYSTEMS OF RESILIENCE IN AGING AND ELDERLY ADULT POPULATIONS

Although the aforementioned behavioral interventions are currently the standard of care for elderly patients susceptible to mood disorders, or who already suffer from one or more, it may be possible in the near future to target biological mechanisms of resilience to protect against stress.

17.1. Stress and Aging in Invertebrates and Mammals

As early as the 1990s, it was known that mutations in the genes of the nematode *Caenorhabditis elegans* (*C. elegans*) led to extensions in their lifespan; it was discovered that these nematodes were resistant to oxidative and thermal stress, as well as other environmental stressors [220]. This ability to face multiple stressors and protect against multiple forms of injury was deemed "multiplex stress resistance" [213]. More thorough molecular observations revealed that mutations that lead to stress resistance involved the slowing of molecular chaperones and cellular protein accumulation, which represents failed homeostasis, and that enhancing chaperone activity *via* enhancement of the heat shock factor 1 (HSF-1) increased stress resilience and life span in *C. elegans* [338]. Though studies in mammals are less numerous, some cell culture work has revealed that fibroblasts from Snell dwarf mice and cells from long-lived species, are resistant to multiple forms of stress in culture [339, 340].

Pharmacologic strategies have also been proposed to improve indices of health and aging, though the effects on resilience have not been consistent [211]. As discussed, the benefits of CR and exercise are large, but committing to a rigorous dietary program is unfeasible for some individuals. Thus, novel research has focused on developing CR mimetics such

as pharmacological approaches in order to confer the benefits of CR and exercise without the rigorous requirements. For instance, the mTOR inhibitor rapamycin has been shown to extend lifespan and have effects on immune processes when administered to mice [341-344], as well as other compounds such as resveratrol and metformin [329]. However, a recent study demonstrated that neither rapamycin nor CR has effects in older mice, and that there may even be deleterious effects to the aging immune system [250]. Resveratrol, a polyphenolic flavonoid found in grapes and red wine, and has been shown to enhance health and increase lifespan, and it may currently be taken as a therapeutic supplement in humans (reviewed in [345]). Other options such as drugs that inhibit the growth hormone/IGF-I axis, or ones that activate specific sirtuins are being discussed as potentially promising candidates to increase lifespan [346].

17.2. Translating Potential Biological Mechanisms to Humans

Given the aforementioned studies in invertebrates and mammals, as well as all that has been discussed in this review concerning the increased understanding of the neurobiology of stress resilience, there seems to be potential in targeting several different pathways to increase resilience in vulnerable populations. In addition to the potential exercise and CR mimetic drugs discussed in the previous section, there is potential to induce changes in biological pathways that have been implicated in resilience. For instance, this review provides evidence for a multitude of systems that are viable pharmacologic targets for increasing stress resistance: targeting the serotonergic system in more acute ways than common SSRIs; the glutamatergic system, and in particular the NMDA receptors as through ketamine administration; AMPA receptors; mGluR receptors; the GABA system; other neurotransmitter systems; and the HPA axis. These biological pathways are complex and integrated, but research has been aimed at uncovering the most effective pathway implicated in stress resilience, which may soon aid in improving health, longevity, and mental capacity, especially in susceptible populations.

CONCLUSION

Frequent exposure to adverse life events is an important risk factor for developing psychopathology. But, why do some individuals succumb to debilitating psychiatric disease whereas others age normally? The notion that gene-by-environment interactions affect susceptibility to stress-related disorders, especially genes enhancing vulnerability is well known. Identifying these genes that confer resilience to stressful events in adulthood has become even more important. In this review, we have provided a brief overview of the biological mechanisms underlying stress resilience, and have explored how resilience changes throughout age. We have also offered suggestions for manipulating these mechanisms to improve resilience throughout life and prevent against stress-induced mood disorders. The topic of resilience as it pertains to the aged population is particularly relevant today, as the US Census Bureau population data projects that by 2030, adults aged 65 and older will constitute nearly 20% of the population [215]. Specifically, Baby Boomers, or those born between 1946 and 1964, are the fastest growing age group in the US [215]. Thus, current research is focusing on how to aid these Baby Boomers as they reach old age to remain healthy and resilient.

While we have focused this review on neurobiological factors of resilience, it is important to emphasize once more that other individualistic factors such as strength, the ability to cope with adversity, optimism, savoring positive experiences, and flexibility also largely contribute to resilient aging [215, 313, 347, 348], as these psychosocial processes are highly integrated with resilience. For example, coping strategies and other psychosocial influences that were briefly discussed in this review are critical components to maintaining resilience. Though a more in-depth discussion of these factors was beyond the scope of this review, they are not trivial and should be considered when evaluating potential psychological interventions in conjunction with biologically-based therapeutics to increase resilience in susceptible populations. In a similar vein, as effective interventions are developed to increase resilience, there must also be a parallel improvement in resilience scales in order to properly capture what elements of health and wellness are being impacted by these interventions. Currently, there are no "gold-standard" resilience scales, as Windle and colleagues found that each of the 15 measures of resilience they reviewed were missing information regarding psychometric properties [349]. Much work needs to be done to most effectively capture resiliency in individuals.

Resiliency research is still in its infancy. It is unlikely that neurobiological mechanisms involved in stress resiliency can be summarized to one single brain structure or target; it is more likely that circuits and systems dynamically drive stress resiliency. Identifying a common circuit involved in drug-induced stress resiliency, such as that induced by a prophylactic ketamine treatment, would be beneficial for the success of future drug development.

We have also discussed here the emerging series of studies that have been conducted to probe the relationship between resilience and aging. Importantly, we prefaced this discussion with a summary of what is currently known about biological mechanisms of stress resilience, and provide suggestions for how to move forward by combining what is currently known about resilience, and how it changes throughout the aging process, to inform more effective preventative resilience-enhancement therapies that is effective throughout life. Ultimately, prophylactic approaches may reduce the worldwide burden of disability, saving billions of dollars a year for countries, and years of emotional and physiological distress for both patients and their loved ones.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

Dr. Christine A. Denny and Josephine C. McGowan are named on non-provisional patent applications for the prophylactic use of ketamine against stress-related psychiatric disorders.

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