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REVIEW ARTICLE

Stress, Depression, Resilience and Ageing: A Role for the LPA-LPA$_1$ Pathway

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Abstract: ***Background*:** Chronic stress affects health and the quality of life, with its effects being particularly relevant in ageing due to the psychobiological characteristics of this population. However, while some people develop psychiatric disorders, especially depression, others seem very capable of dealing with adversity. There is no doubt that along with the identification of neurobiological mechanisms involved in developing depression, discovering which factors are involved in positive adaptation under circumstances of extreme difficulty will be crucial for promoting resilience.

***Methods*:** Here, we review recent work in our laboratory, using an animal model lacking the LPA$_1$ receptor, together with pharmacological studies and clinical evidence for the possible participation of the LPA$_1$ receptor in mood and resilience to stress.

***Results*:** Substantial evidence has shown that the LPA$_1$ receptor is involved in emotional regulation and in coping responses to chronic stress, which, if dysfunctional, may induce vulnerability to stress and predisposition to the development of depression. Given that there is commonality of mechanisms between those involved in negative consequences of stress and in ageing, this is not surprising, considering that the LPA$_1$ receptor may be involved in coping with adversity during ageing.

***Conclusion*:** Alterations in this receptor may be a susceptibility factor for the presence of depression and cognitive deficits in the elderly population. However, because this is only a promising hypothesis based on previous data, future studies should focus on the involvement of the LPA-LPA$_1$ pathway in coping with stress and resilience in ageing.

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1. INTRODUCTION

Stress, particularly chronic stressful life events, may have a negative impact on mental health, being the main environmental risk factor in the aetiology of depression [1, 2].

Stress has impacts at all ages, but due to the life changes faced by the elderly and the neurobiological modifications that take place during this stage, stress may have particularly negative effects on older people [3]. Moreover, continuous exposure to stressors over the years, involving brain reorganization, also known as allostatic load [4], has been linked to depression in later life [5].

In the elderly population, mood disorders, the most common source of psychiatric morbidity [6], are likely to be associated with increased risk for mild cognitive impairment (MCI) and dementia [7], including Alzheimer's disease (AD) [8], and contribute to several medical conditions with poor clinical outcome, relapse and incomplete recovery [6]. However, not all elderly people develop psychopathological disorders, and some can even have an adaptive response despite difficulties and age-related changes in the brain [8]. This resistance to the deleterious effects of stress is known as

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resilience [9]. Key insights from stress studies include understanding the factors that promote the adjusted pattern of responses and successful coping with adversity, information that is crucial to finding new potential therapeutic targets in the future.

The LPA pathway and specifically the LPA_1 receptor may be one such factor. This receptor is one of the six G protein-coupled receptors through which lysophosphatidic acid (LPA, 1-acyl-2-sn-glycerol-3-phosphate) acts. The brain distribution of the LPA_1 receptor in key emotion-processing regions, which overlap with those frequently implicated in ageing processes [10], places it in an ideal situation to control the impact of stress on behaviour and neurobiological variables and to regulate the affective states. In fact, it has recently been shown that the LPA_1 receptor is involved in emotional regulation [11], in the coping response to chronic stress [12, 13] and probably in the pathogenesis of depression [14].

The accumulated evidence reviewed below reveals a role for the LPA_1 receptor in mood and resilience to stress, and the alteration of this receptor may be a susceptibility factor for the presence of depression and cognitive deficits in the elderly population.

2. NEUROBIOLOGY OF STRESS COPING, DEPRESSION AND AGEING

From a neurobiological perspective, there are marked similarities between stress and ageing [15]. In both conditions, the whole brain, shows volumetric alteration indicating atrophy [16-18], and white matter becomes less dense and loses integrity [16, 18, 19]. Beyond impacting the overall brain volume, the limbic system is particularly affected by stress and ageing [20]. Thus, along with other regions, the hippocampus constitutes a target structure of the adverse effects of stress and is directly involved in endocrine responsiveness and indirectly related to immune responses [21] and emotional and motivational impairment, core symptoms of depression [22]. Similarly, brain ageing is characterized by several neurobiological modifications, particularly in the hippocampus [18, 23].

Chronic stress leads to dysregulation of the hypothalamic-pituitary-adrenal axis, subsequently resulting in enhanced levels of glucocorticoids [24]. Cumulative lifetime exposure to corticosterone (CORT) plays an important role in the hippocampal ageing process [25]. Moreover, ageing increases basal levels of corticosterone in the brain [26], particularly in the hippocampus [27]. Glucocorticoids are involved in a subset of stress and aged-induced functional disturbances [26]. An example of these alterations is the impact on neurogenesis. In fact, strong evidence has indicated that both stress and ageing have been associated with reduced neurogenesis [28, 29]. Most studies conclude that stress and corticosterone treatment reduce hippocampal cell proliferation [29], differentiation, and maturation and the survival of newborn hippocampal cells [30, 31]. With some exceptions, recent studies have shown that various strategies to disrupt neurogenesis induce effects reminiscent of either anxiety or depression [32, 33] and may be at least partly responsible for stress-related depression [33] and ageing-related memory deficits [34, 35]. Adult-born hippocampal neurons are, in turn, eventually essential for normal expression of the endocrine stress response [33, 36, 37].

Increased glucocorticoid levels and reduced neurogenesis are two interdependent and interrelated processes [38, 39] that, at the same time, are linked to other pathological changes that take place in stressed and ageing brains [40, 41]. Thus, one of the key processes responsible for damage to hippocampal structural integrity is oxidative stress, in which the endocrine system seems to play a role [42]. This implies that frequent and sustained activation of the hypothalamic-pituitary-adrenal axis could promote oxidative damage [43]. Enhanced vulnerability to oxidative stress constitutes a critical factor in age-related hippocampal changes [44-46].

In both stress and ageing, the other major mediator of cellular damage of key brain structures such as the hippocampus, aside from oxidative stress, is the inflammatory response, which can act synergistically with oxidative stress [47-49]. Although an increase in corticosteroid levels does not necessarily involve enhanced inflammatory activation [50], stress and elevated and sustained corticosteroid levels have been associated with increased inflammation in the CNS [47, 50]. Thus, it is becoming well established that pro-inflammatory cytokines activate microglia and astrocytes, promote local inflammation, and cause oxidative brain damage, particularly in the hippocampus [51-55]. For this reason, classically intense inflammatory activation has been associated with impairing neuroplasticity and neurogenesis, which can lead to depression. Nevertheless, the connections among stress, inflammation and depression are far from being a simple correlation. Recent studies indicate that impairment, rather than upregulation, of the normal structure and function of microglia [56], could be found following exposure to certain forms of chronic stress and in particular in ageing [57], during which microglia display dystrophic morphology, and with increases in senescent cells [58, 59], which may lead to reductions in total glia and proliferating microglia [60-63]. Notably, deviations from the normal microglial activation status have been associated with a high prevalence of major depression [56, 61, 64].

In this complex interaction among interconnected factors that are at least partly responsible for the reduced volume of hippocampus, the excitation-inhibition balance that further complicates the situation seems to be key for the control of the stress system [65, 66] and of brain ageing [67-69]. Elevated CORT secretion after stress may be responsible for the changes in glutamate/GABA cycling, shifting its balance in hippocampal neurons [70]. Further, GABA and glutamate play a major role in central integration of HPA stress responses [67, 71]. At the same time, dysregulation of excitatory and inhibitory signalling has been associated with oxidative stress [72] in both stress [73] and ageing [74] and with microgliopathy-associated depression in rodents [56, 75].

Taken together, a comprehensive understanding of neurobiological mechanisms of the reduction of hippocampal volume and the atrophy observed in certain brain areas after intense and long-lasting stressing situations [76] requires the consideration of numerous interdependent factors. However,

irrespectively of the processes responsible for the hippocampal damage, it has become clear that the reduction of hippocampal volume correlates with the frequency of depressive episodes in people with recurrent depression [77-80]. Moreover, hippocampal atrophy is associated with severe and persistent depression in older patients [81].

Altered hippocampal function, in turn, may influence the activity of neural circuitry in the prefrontal cortex (PFC) and amygdala [82, 83].

The PFC is one of the brain regions most susceptible to experience-dependent change [84]. While the PFC is highly involved in stress resilience, it is also extremely vulnerable to the impact of stress [84], and with ageing, it becomes less functionally efficient [70, 85]. Likewise, in mood disorders, which are often precipitated by stressful experiences, changes in PFC mediate a loss of resilience [85] that is aggravated by the age-related changes [86]. As reviewed above, in the PFC, the interconnected factors responsible for the reduction of hippocampal volume also appear to play a role in stress-induced biological changes [16, 80, 87, 88].

Given that the mPFC has extensive downstream projections to regions of the limbic system such as the amygdala [89], providing a substrate for downstream regulation of emotion [90], as well as influences on hypothalamic-pituitary adrenal (HPA) activity [91], changes in this region are manifested at several levels, including impaired glucocorticoid-receptor-mediated negative feedback [92], disrupted working memory and maladaptive responses in the face of adversity [84, 93]. This implies that changes in mPFC neurons projecting to the amygdala interact with the impact of stress in this limbic region, thereby increasing the magnitude of negative effects and the reactivity of the amygdala [84, 89]. Loss of the excitatory/inhibitory balance, tipping the equilibrium in favour of increased excitability, may be mechanistically involved in this process [94, 95]. Moreover, excessive limbic activation, specifically amygdala hyperactivation, results in exaggerated CORT release after negative events that would perpetuate the problem, and hence may affect the ability to regulate emotion [96]. This is associated with a negative mood bias and maladaptive processing of emotional stimuli, resulting in long-term depressive dysfunction and symptoms of anxiety [97].

Together, because the PFC, amygdala, and hippocampus are interconnected and influence each other *via* direct and indirect neural activity [89, 98-102], stress and ageing may modify the dynamic network connectivity [103-105]. Dysfunctional changes within the highly interconnected 'limbic' regions have been implicated in depression [96, 104] and are particularly relevant in the case of late-life depression [82].

It is therefore noteworthy that identifying factors involved in the functionality of the limbic system and in stress-induced changes may provide new therapeutic targets and further promote resilience in at-risk populations, particularly in the elderly. LPA, mainly through the LPA$_1$ receptor, may be one such factor. Here, we review integrated human and animal findings suggesting the possible involvement of this signalling pathway in stress-induced changes and adaptive responses to adverse life events.

3. LPA, LPA$_1$ AND THE LIMBIC SYSTEM

LPA is an endogenous simple bioactive phospholipid that exhibits several biological functions acting through six well-characterized and widely distributed G protein-coupled receptors, *i.e.*, LPA$_{1\text{-}6}$ [106, 107]. Recently, two additional receptors (GPR87 and P2Y10) have been proposed to may be responsible for LPA [108, 109]. Lately, LPA has emerged as a regulatory molecule in the brain, acting mainly through the LPA$_1$ receptor [107, 110]. This receptor activates multiple intracellular signalling pathways, such as the Rho, PPC, Ras and PI3K pathways (reviewed in Riaz *et al.* [111]). The anatomical distribution of LPA$_1$ receptors has been described both in adult rodent and in human, using functional [35S]GTPγS autoradiography and immunohistochemical procedures, respectively. The highest density of LPA$_1$ receptors was observed in myelinated areas of white matter such as the corpus callosum and internal capsule but also in the hippocampus, frontal cortex, amygdala and striatum [112-117], key emotion-processing regions [118], which are also associated with the ageing process [10].

Studies describing the brain architecture of mice null for LPA$_1$ receptor have reported reduced brain volume and white matter disintegration [114, 119, 120], which may lead to negative outcomes regarding the capacity for flexible adaptation to face environmental challenges [12, 13].

Experiments with knockout animals revealed a role for the LPA$_1$ receptor in maintaining the morphology and function of the limbic system. The absence of the LPA$_1$ receptor changes the structure and plasticity of the CNS, with particularly strong effects on the hippocampus [12, 13, 117, 120], mPFC and amygdala [11, 14] as revealed by the behavioural outcome in null mice. Thus, in tasks that rely on hippocampal function, such as the Morris water maze [117, 121], the hole board test, in which the long-term components of working memory are required [122, 123], and object recognition tasks [124] suggest that the hippocampus malfunctions in the absence of the LPA$_1$ receptor [117, 121]. Neurobiological evidence indicates that this is in fact the case [117, 124]. Null animals exhibit abnormalities in the hippocampal structure, synapse formation and plasticity [12, 117, 120]. Further, reduced amygdala volume and impaired mPFC function have also been reported [11].

However, it should be noted that the brain is structurally and functionally organized into a complex network that facilitates the efficient integration and segregation of information processing and behaviour regulation [125-127], fueling significant interest in the role of dysfunctional connections in the pathophysiology of neuropsychiatric diseases. Animals lacking the LPA$_1$ receptor displayed impaired functional brain maps, showing increased limbic system activation [11] and defective connectivity patterns [11, 14]. Although this description is derived from brain functional mapping, it could also be extrapolated from behavioural performance. Thus, the impairment in LPA$_1$-null mice of fear extinction, a phenomenon of experience-dependent plasticity that depends on the level of function of the corticolimbic circuit, with an emphasis on the amygdala, prefrontal cortex, and hippocampus [127-129] provides additional evidence of the involve-

ment of the LPA_1 receptor on the integrity of circuits involved in emotional regulation [11].

Furthermore, the absence of the LPA_1 receptor alters adult neurogenesis in the hippocampus [12, 117], which, as indicated above, could be a cause of altered hippocampal function; consequently, it affects the integrity of the limbic system.

4. LPA_1 RECEPTOR AND NEUROBIOLOGY OF STRESS

Recent evidence also suggests a role for the LPA_1 receptor in mediating the consequences of stress in the hippocampus. In fact, the lack of LPA_1 signalling confers vulnerability to chronic stress, which precipitates hippocampal pathology, exacerbating the stress-induced reduction in neurogenesis and increase in apoptosis [12]. Thus, the absence of this receptor results in a phenotype of low resilience. To date, there is insufficient available information to support the pathway through which the LPA_1 receptor may be involved in this adaptation. However, several results from our group can help to outline some possible mechanisms. In this context, the absence of the LPA_1 receptor induces exaggerated endocrine responses to emotional stimuli [11] and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis after chronic stress [12] that could lead to oxidative damage in the hippocampus [130]. In fact, LPA_1-null mice display increased oxidative stress, which may be involved in the hippocampal abnormalities observed in this genotype after chronic immobilization, including neurogenesis deficits, and increased apoptosis [14]. Moreover, the absence of the LPA_1 receptor induces changes in glutamate and GABA signal transmission, resulting in further basal strengthening of the hippocampal glutamatergic synapses [121] and reduced GABAergic neurotransmission in the hippocampus [Rosell-Valle *et al.* Unpublished data] and in the amygdala, which may at least partially explain the increased activation of the limbic system [11, 14, 131, 132] and likewise the induction of CORT release due to connections with hypothalamus [133].

As reviewed above, several lines of evidence implicate microglial dysfunction as a key mechanism of neurogenesis suppression under stressful conditions [64, 134-136] and ageing [58, 137-139]. Given that microglia from mouse or rat mainly express LPA_1 and/or LPA_3 receptor [140, 141], whereas human microglial cell lines express $LPA_{1\text{-}3}$ receptors [140, 142], it is not unreasonable to assume that LPA may have a role in regulating microglial activation and that the absence of LPA_1 receptor may induce microglial pathology. However, this hypothesis should be interpreted cautiously and remains an active area of research. Moreover, several caveats exist when studying the inflammatory properties of LPA. Thus, while a large body of research provides strong evidence for an inflammatory response induced by LPA [140, 142, 143] activating and polarizing microglia towards a pro-inflammatory M1-like phenotype [144], other studies do not lend support to the inflammatory role of LPA and even suggest anti-inflammatory properties of this lipid [145]. In this context, overexpression of autotaxin in microglia, which entails an increase in LPA levels, protects the cells from oxidative stress by increasing the level of catalase [146] and decreases the inflammatory response at least partially through an upregulation of IL-10 [146, 147]. This seeming contradiction might reflect a remarkable heterogeneity in the responses of microglia to LPA; these responses depend on the cellular preactivation experience and may vary across microglial maturation states, activation states, and species sources [148]. Understanding the complex mechanism of microglial activation induced by LPA, which may be modified either at the level of LPA synthesis (using, *e.g.*, ATX inhibitors) or at the level of signal transmission (LPA receptor agonists [144]) apart from LPA_1 receptor antagonism [141], might provide new pathophysiological and therapeutic insights into stress-related and ageing-related disorders.

5. LPA/LPA_1 PATHWAY, DEPRESSION AND RESILIENCE

Stress constitutes the major environmental risk factor in the aetiology of depression, and the resulting characterization of knockout animal evidence yields a role for the LPA_1 receptor in the pathogenesis of depression. Indeed, recently, based on validity criteria (face, construct and predictive) [149] and considering the results of accumulated data with studies using animals lacking the LPA_1 receptor, our group have proposed maLPA_1-null mice as an animal model of mixed depressive-anxiety phenotype [14].

However, although knockout models are indispensable instruments for establishing the functions of a receptor, validation with pharmacological studies is necessary to assess the contribution of a signalling pathway to a disease. Indeed, injections of 18:1 LPA, a LPA species with high affinity for the LPA_1 receptor [150-153], increased the immobility in the forced swimming test, a parameter that has been associated with depressive-like behaviours [154]. Consistent with those results, after acute ICV infusion of 18:1 LPA (0.15-1.5 nmol), mice showed increased anxiety-like behaviours in both the elevated plus maze and the hole-board test [155]. Compared with studies using knockout animals, some, though not all, of the pharmacological studies produced apparently contradictory data. Timing mechanisms may explain the divergent results between knockout models and pharmacological studies. Thus, the functional antagonism of LPA_1 by a high concentration of LPA agonist is probably due to receptor internalization [156, 157], that being a mechanism dependent upon LPA concentration [158].

Furthermore, as predicted from *in vitro* studies, the LPA_1 receptor may be a target of pharmacological treatment with antidepressants (such as tricyclic and tetracyclic and selective serotonin or noradrenaline reuptake inhibitors), and it may be involved in the actions of these drugs and thus in some of their therapeutic actions [14, 159, 160]. In addition, gintonin, a novel lysophosphatidic acid (LPA) receptor-activating ligand from ginseng, acts as an antidepressant, probably as a result of an increment of serotonin [161]. Moreover, because neurogenesis is required for some of the behavioural effects of antidepressants, and given that LPA_1 is expressed by a defined population of neural precursor cells in the hippocampus [115], the modulation of neurogenesis by this receptor [115, 117], without ruling out other mechanisms, may confer an antidepressant-like response. Moreover, it should be noted that it is likely that specific types of depression may be more frequently associated with higher or

lower levels of microglial activation [56], and under some circumstances, antidepressant drugs induce an increase, rather than a decrease, in tumour necrosis factor (TNF-α) and interleukin-6 (IL-6) levels [162]. Given that LPA can induce TNF-α release [163, 164] and IL-6 production [142, 164, 165], the modulation of microglia by LPA may be used as antidepressive approach, at least in specific types of depression.

Translation of findings about a receptor to coping with stress and mood control is necessary. Accordingly, polymorphism in the LPA_1 receptor has been related to augmented risk of essential hypertension. Given that stress, which is the main environmental cause of depression, increases the susceptibility of patients with risk alleles [166], genetic variants in this receptor may participate in the aetiology of depression. In fact, after chronic and unpredictable stress, a reduction of LPA_1 receptor (EDG-2, endothelial differentiation, lysophosphatidic acid G-protein coupled receptor 2) was observed, and this reduction could be reverted by antidepressant treatment [167]. Moreover, in patients with major depression, the expression of LPA_1 (EDG-2) was reduced 3- or 4-fold in temporal cortex [168].

Alternatively, it may be pertinent to ask whether increased expression of the LPA_1 receptor is correlated with positive mood and may be involved in adaptively overcoming stress. Based on current evidence, the expression of this receptor is more likely related with high mood states. In fact, although there is cross talk between blood and some, though not all, brain regions, the LPA_1 receptor gene (edg2) has been used as a biomarker for high mood states [169]. Moreover, a longitudinal study of depressed patients undergoing cognitive behavioural therapy [170], 5 genes considered as biomarkers for high mood, including the LPA_1 receptor gene (edg2), and 5 genes related to low mood were evaluated before and after therapy. The expression of these genes discriminated patients and controls with high sensitivity, and clinical improvement was associated with a greater ratio of high mood markers to low mood markers [170].

Understanding the mechanisms involved in resilience is of critical relevance, not only for promoting coping mechanisms but also to reduce the effect of negative stress and to prevent maladaptive responses, which are responsible for developing neuropsychiatric disease. Clinical experimental evidence for the participation of the LPA_1 receptor in resilience is still limited, but on-going studies are beginning to reveal its possible involvement in positive mood. Such studies synergize with advances in animal-model studies revealing that reduced expression of the LPA_1 receptor increases the vulnerability to negative consequences of stress. Altogether, these data identify the LPA_1 receptor as a strong candidate for mediating the central effects of LPA on emotion and indicate that it may be involved in promoting normal behavioural function in the face of stress and that LPA_1 dysfunction may induce vulnerability to stress and predispose individuals to develop depression (Fig. **1**).

6. LPA, LPA$_1$, AGEING AND RESILIENCE

As indicated above, the complex linkage of the LPA/LPA_1 receptor-signalling pathway with a variety of factors involved in neurobiology of stress, which overlap with those frequently implicated in ageing processes [11], and which may contribute to ageing-related diseases such as depression, cognitive deficits, and AD in some older individuals [15, 48], suggests the possibility of the functional deterioration of this pathway in an age-dependent manner. However, to date, attempts to understand the involvement of the LPA/LPA_1 receptor-signalling pathway on ageing and age-related decline in brain function have been insufficient.

One of the primary motivations for focusing on the LPA pathway in ageing is the observation that ageing itself is a variable in determining the specific phospholipid composition of the brain [171]. Moreover, the expression of edg2 has been shown to decrease with age, and this decrease was almost entirely prevented by caloric restriction [172], a strategy that prevents age-associated diseases and has been associated with longevity [173], as well as improvement of biomarkers of ageing such as reduced metabolic rate and oxidative stress and recovery of neuroendocrine disturbances [174]. In addition, it has been observed anti-aging properties of LPA by improving the oxidative resistance [175].

Additionally, the ERK1/2 pathway has recently been considered as a protective mechanism against oxidative stress and inflammation [176], dysfunction of which has been related to late-life depression [176, 177]. Activation of the Gi/o-coupled LPA1 is involved in the stimulation of ERK1/2 signalling by tricyclic and tetracyclic antidepressants [159, 160]. It has been previously reported that low levels of ERK1/2 have been observed in several stress-related brain areas after chronic stress [178, 179] and in the hippocampus of animal models of pathological ageing or AD [180]; thus, the LPA_1 receptor may play a protective role in these pathological conditions. Furthermore, the proper function of the LPA-LPA_1 pathway may also act as a protective factor against developing hypertension [165] and cerebrovascular alterations [181], both of which are also involved in depression in the elderly [182-184].

Studies in AD provide another indirect but notable example of the possible participation of the LPA/LPA_1 receptor-signalling pathway on late-life depression and resilience in the elderly. Thus, AD may be considered as a condition in which there is a loss of neuroplasticity [185, 186]. This process is unique to each individual and provides the critical substrates for adaptation to changing situations, a condition necessary for responding adaptively to challenges. In this context, the expression of autotaxin, the enzyme responsible for LPA synthesis, is enhanced in MCI and AD patients [187, 188], where it has been related with a reduction of LPA_1 expression [189]. Moreover, the concentrations of autotaxin in AD predicted the metabolic rate, the thickness of cortical areas and the performance on executive and memory tasks [188]. Thus, with higher levels of autotaxin, the metabolism in the medial temporal lobe and PFC was slower, the PFC was thinner, and the performance on executive and memory tasks was worse, these being cognitive functions that also seem to be affected in depression [190, 191].

Moreover, it has been shown that in AD brains, LPA activates GSK-3, one of the kinases involved in Tau hyper

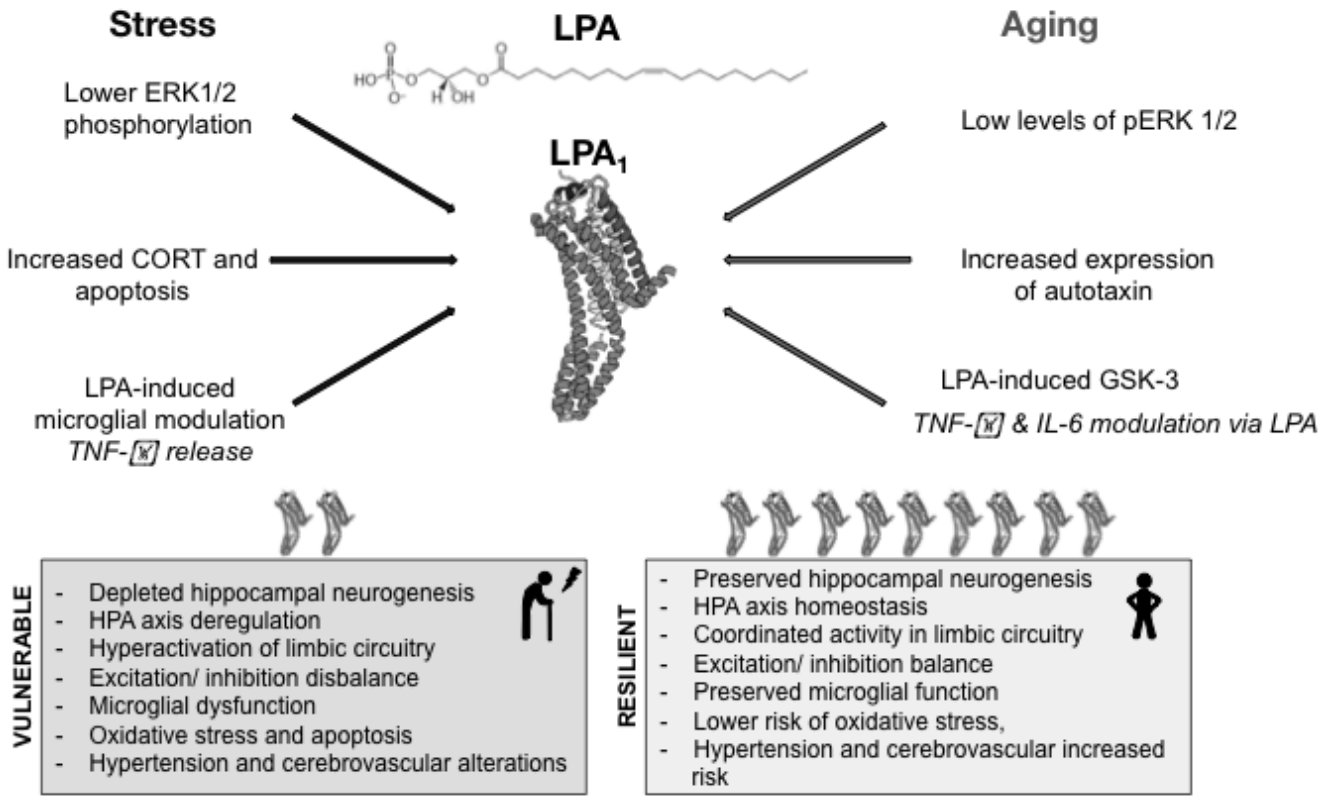

Fig. (1). The LPA-LPA_1 pathway: convergent mechanisms in both stress and aging. This pathway is linked to vulnerable or resilient individuals.

Table 1. Relevant studies connecting the LPA_1 receptor and the LPA-LPA_1 pathway with stress, depression and ageing.

Stress and Depressive Behaviour		
Reference	**Species**	**LPA-LPA_1 Pathway Findings**
Castilla-Ortega *et al*. [12]	Mouse	The absence of LPA_1 aggravates the noxious effect of chronic stress on hippocampal neurogenesis and spatial memory
Pedraza *et al*. [11]	Mouse	Stress hyperreactivity in the absence of LPA_1 receptor (CORT and FST)
Moreno-Fernández *et al*. [14]	Mouse	Mice lacking the LPA_1 receptor display an anxious-depressive phenotype and increased limbic-system activation, similar to that observed in depressive patients. Reversible by antidepressant treatment.
Kim *et al*. [161]	Mouse	LPA_1 ligand gintonin alleviates depressive-like behaviour (FST)
Castilla-Ortega *et al*. [154]	Rat	LPA 18:1 reduced anxiety and dose-dependently increased immobility time in FST
Xu *et al*. [166]	Human	Polymorphism of LPA_1 receptor has been related to higher risk of essential hypertension in the presence of stress
Aston *et al*. [168]	Human	Reduced expression of the LPA_1 gene (edg2) in the temporal cortex of patients who suffered from depression
Kéri *et al*. [170]	Human	LPA_1 gene expression in peripheral blood as a biomarker for high mood in depressive patients treated with CBT
Aging		
Sun *et al*. [175]	Yeast cells	LPA has anti-aging and anti-oxidative stress, similar to that observed after resveratrol treatment
Kim *et al*. [198, 199]	Mouse	LPA_1 ligand gintonin increases hippocampal neurogenesis and prevents cognitive symptoms in an animal model of AD
Pan *et al*. [172]	Human	The expression of edg2 (LPA_1) decreased with age
Lloret *et al*. [195]	Human	LPA activates GSK-3 and is involved in Tau hyperphosphorylation and thus in molecular pathways in pathological ageing (AD)
McLimans *et al*. [188]	Human	Higher levels of autotaxin in MCI and AD

Abbreviations. AD, Alzheimer's disease, CBT, cognitive-behavioural therapy; EDG2, endothelial differentiation, lysophosphatidic acid G-protein-coupled receptor, 2; FST, forced swim test; MCI, mild cognitive impairment.

phosphorylation [192], a neuropathological component of intraneuronal neurofibrillary tangles [193-195].

Additionally, in a transgenic mouse AD model characterized by displayed Aβ1-40-induced short- and long-term memory impairment, long-term oral administration of gintonin, reduced amyloid plaque deposition. Moreover, Aβ1-40-induced cognitive dysfunction was rescued by gintonin [196]. On the other hand, it has been established that hippocampal neurogenesis may play a role not only in the age-related decline of cognitive function but also in neurodegenerative diseases such as AD. However, further studies are needed to confirm these results. Oral administration of gintonin increased hippocampal cell proliferation and improved brain functions, including learning and memory, in an animal model of AD [197, 198], an effect that seems to be mediated by the stimulation of neurogenesis *via* LPA_1 receptor activation [197, 199]. These data support the application of gintonin for the prevention or treatment of cognitive decline in elderly people and patients with neurodegenerative diseases such as AD.

In conclusion, experimental evidence for the participation of the LPA-LPA_1 receptor pathway in late-life depression remains limited but was recently provided by the implication of this pathway in pathological conditions that present cognitive deterioration and depression (Table **1**).

CONCLUSION

Both ageing and chronic stress are associated with altered brain plasticity and an increased risk of developing brain disorders [15]. Given that the LPA_1 receptor is distributed in key emotion-processing regions of the brain, overlapping with regions frequently implicated in aging processes, and given its participation in brain plasticity, this receptor is in an ideal situation to control the impact of stress on behaviour and neurobiological variables and to regulate the affective state, particularly in ageing.

The LPA/LPA_1 receptor-signalling pathway clearly participates in the mood regulation and resilience to stress, and the alteration of this pathway may be a susceptibility factor for the presence of depression.

Regarding its participation in ageing, recent data suggest that the LPA/LPA_1 receptor-signalling pathway is a promising mechanism implicated in resilience to ageing, the dysregulation of which may be involved in late-life depression. Other tantalizing connections continue to be reported, but we must remain cautious as to whether this is merely a hypothesis based on previous data that require future verification. Therefore, further research should be focused on the participation of the LPA/LPA_1 receptor-signalling pathway in late-life depression and resilience in the elderly, allowing the development of drugs and therapeutic targets that may be useful for intervening to enhance resilience and mitigate risk of stress-related psychiatric disorders.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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