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PPARγ and Stress: Implications for Aging

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Abstract

Complex interactions link psychological stress and aging - stress generally promotes aging processes, and conversely, aging can contribute to stress dysregulation. Stress and aging have remarkably similar effects on brain. Both induce neuroinflammation and alter neuronal metabolism and activity, which to varying extents are causally-linked to the development of stress and aging pathology. As such, induction of one or more of these brain disturbances by either stress or aging could predispose for the development of dysfunction in the other. Notably, peroxisome proliferator-activated receptor γ (PPARγ) is expressed in brain regions that regulate both stress and aging (e.g., hippocampus) and can act to prevent the consequences of aging and stress on the brain. In addition, PPARγ agonists reduce the physiological stress response itself. Thus, PPARγ may represent a critical mechanistic link between brain aging and stress that could hold therapeutic potential for the prevention and treatment of age-related cognitive and mood disorders.

Keywords

Stress; Aging; Corticosterone; PPARγ; Brain; HPA axis

1. Introduction

Aging is marked by a high degree of variability, with some individuals exhibiting little-to-no loss of function (‘successful’ aging), while others suffer significant loss of function (‘unsuccessful’ aging). Among the genetic and environmental factors linked with unsuccessful aging, exposure to stress (i.e., a real or perceived threat to homeostasis or well-being), and dysregulated physiological responses to stress (e.g., excessive glucocorticoid exposure), have received considerable attention over the last several decades, particularly in relation to promoting age-induced cognitive decline (Wise et al., 1997; Aguilera, 2011; Garrido, 2011). More recently, it has been shown that psychological stress activates brain peroxisome proliferator-activated receptor γ (PPARγ) signaling, which in turn can regulate brain inflammatory and metabolic processes, perhaps providing some degree of neuroprotection from stress (Garcia-Bueno et al., 2005; Garcia-Bueno et al., 2007; Garcia-

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Bueno et al., 2008). Moreover, brain PPARγ signaling is capable of attenuating physiological stress responses (Ryan et al., 2012). This review summarizes the current state of the field, and further proposes that PPARγ may represent a critical mechanistic link between brain aging and stress processes.

2. Stress and aging

2.1 Stress and the HPA axis

During psychological stress the brain orchestrates a series of physiological and behavioral responses to promote survival (reviewed in: Ulrich-Lai and Herman, 2009). These physiological responses include a rapid activation of the sympathetic branch of the autonomic nervous system that results in numerous catecholamine-mediated effects throughout the body, such as increased heart rate and blood pressure. Activation of the hypothalamic-pituitary-adrenocortical (HPA) axis occurs a bit more slowly, with parvocellular neurons in the paraventricular nucleus of the hypothalamus (PVN) releasing corticotropin releasing hormone (CRH) and vasopressin, thereby driving the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary into the general circulation. Upon reaching the adrenal cortex, ACTH stimulates the production and release of glucocorticoids (e.g., cortisol in humans and corticosterone in rats and mice) into the bloodstream. Glucocorticoids then promote widespread effects via actions on glucocorticoid and mineralocorticoid receptors throughout the brain and body, including mobilization of stored energy, maintenance of vasomotor tone, and negative feedback to inhibit further HPA axis activation. These physiological responses to stress are coordinated by a highly-interconnected network of numerous brain structures, including several hypothalamic nuclei, prefrontal cortex, hippocampus, amygdala, and the bed nucleus of the stria terminalis. Importantly, while these stress responses are critical for immediate survival in the face of stress, excessive or prolonged activation is associated with a number of deleterious side effects, including increased neuronal vulnerability to insults, particularly in brain regions that express high levels of glucocorticoid and mineralocorticoid receptors (e.g., hippocampus and prefrontal cortex; reviewed in: Wise et al., 1997; Garrido, 2011).

2.2 Contribution of aging to dysregulation of the HPA axis

While the hallmark characteristic of the HPA axis is its activation by stress, the system also maintains a lower basal level of activity in the absence of stress that varies throughout the circadian rhythm. In this manner, plasma glucocorticoids are generally lowest in preparation for sleep (i.e., nadir) and highest in preparation for awakening (i.e., peak). During aging, this circadian glucocorticoid rhythmicity is often disrupted. For instance, a large proportion of healthy, aged humans show either elevated basal cortisol levels throughout the entire day (Lupien et al., 1996), or specifically at the nadir of the circadian rhythm (Magri et al., 2000; Ferrari et al., 2001), leading to a flattening of the circadian fluctuations. Similarly, elevations in basal corticosterone levels during the circadian rhythm have generally been reported in rodent studies, though the proportion of those affected varies according to strain and particular experimental conditions (reviewed in: Wise et al., 1997; Aguilera, 2011; Garrido, 2011). Such circadian disruptions can lead to glucocorticoid levels that are inappropriate to the time of day, and may result in excessive overall glucocorticoid exposure.

Aging can also be accompanied by altered HPA axis activation in response to stress. For instance, older people may have a greater and/or more prolonged plasma cortisol response (reviewed in: Ferrari et al., 2001), and it likewise has been reported that aging rodents often exhibit an elevated and/or persistent corticosterone response to stress (Wise et al., 1997; Herman et al., 2001). This may be due in part to a reduction in glucocorticoid negative

feedback that can occur during aging in both people (reviewed in: Ferrari et al., 2001), and rodents (reviewed in: Wise et al., 1997), thereby impairing the ability of the HPA axis to terminate its own response. In this manner, prolonged stress responses can contribute to excessive glucocorticoid exposure during aging.

Both the inappropriate glucocorticoid rhythmicity and prolonged stress responses likely result, at least in part, from aging processes in the brain regions that regulate the HPA axis. For instance, prefrontal cortical, and to a lesser extent hippocampal and amygdalar, volume decreases with aging (reviewed in: Raz and Rodrigue, 2006). In older rats, the prefrontal cortex appears to be less able to constrain HPA axis responses to stress (Garrido et al., 2012), suggesting a deterioration of the brain network that normally regulates stress responses. Moreover, expression of glucocorticoid and mineralocorticoid receptors in the rat prefrontal cortex, hippocampus and hypothalamus is reduced during aging, as is glucocorticoid-mediated receptor translocation (Mizoguchi et al., 2009), suggesting that reduced glucocorticoid signaling in these brain regions may contribute to impaired glucocorticoid negative feedback at the level of the brain.

2.3 Contributions of the HPA axis to aging-associated impairments

Dysregulated HPA axis activity, like that described above, may further contribute to aging processes (Wise et al., 1997; Aguilera, 2011; Garrido, 2011). For example, elderly subjects whose basal cortisol levels increase with age show greater cognitive decline (Lupien et al., 1994; Ferrari et al., 2001). Similarly, disrupted basal cortisol levels during aging are associated with greater loss of hippocampal volume (Magri et al., 2000). Moreover, plasma cortisol appears to be beneficial for hippocampal and prefrontal brain activity during challenging cognitive tasks in young subjects, but is detrimental in older subjects (Kukolja et al., 2008). Taken together, these studies suggest that inappropriate stress responses may contribute to cognitive decline and brain aging.

3. PPARγ and aging

3.1 PPARγ overview

PPARγ is a member of the nuclear hormone receptor superfamily of ligand-activated transcription factors. It forms a heterodimer with the retinoid x receptor (RXR) to bind to specific response elements in the promoter region of its target genes. In the absence of agonist ligands, co-repressor complexes are recruited to blunt PPARγ transcriptional activity. Conversely, in the presence of agonist ligands, co-repressors are released and transcriptional co-activators are recruited; this is associated with increased transcription of target genes (reviewed in: Berger and Moller, 2002; Semple et al., 2006). In addition to its regulation by co-activators and co-repressors, PPARγ signaling is also modified by post-translational modifications including sumoylation (e.g., Ohshima et al., 2004), ubiquitination (e.g., Hauser et al., 2000), and phosphorylation (e.g., Choi et al., 2010; reviewed in: van Beekum et al., 2009).

Despite many years of investigation, a high-affinity physiological agonist ligand for PPARγ has not yet been reported. Rather, various fatty acids, fat metabolites, and inflammatory lipid mediators bind to it with moderate affinity (e.g., Kliewer et al., 1995; Baker et al., 2005; Schopfer et al., 2005) to regulate gene expression. This has led to the suggestion that perhaps there is in fact no high-affinity endogenous agonist, but rather the physiological role for PPARγ is to act as a general physiological sensor for the flux of fatty acids and related molecules (Semple et al., 2006). Consistent with this, PPARγ regulates the expression of a host of genes involved in lipid and glucose metabolism, and can also act as a potent anti-inflammatory agent via indirect interactions with other transcription factors (Jiang et al., 1998; Ricote et al., 1998).

High affinity pharmacological agonists of PPARγ have been produced. These include the thiazolidinedione (TZD) class of insulin-sensitizing drugs (Lehmann et al., 1995), e.g., Rosiglitazone and Pioglitazone, that until recently were widely prescribed for the treatment of type-2 diabetes. Several studies discussed in this review have used TZDs to manipulate PPARγ signaling, providing important insight into its potential role in stress and aging pathology. In this context, however, it is necessary to consider the caveat that PPARγ agonists could have off-target effects and that in many cases loss-of-function studies have not yet been performed to confirm PPARγ's role.

PPARγ is highly expressed in white adipose tissue, where its activation leads to proliferation of white fat cells (Tontonoz et al., 1994). As such, PPARγ is considered to be a master regulator of adipogenesis, and its role in white adipose tissue has been extensively studied. Although its expression in non-adipose tissue is considerably lower, it is now appreciated that PPARγ regulates metabolism and/or inflammation in macrophages (e.g., Ricote et al., 1998), vascular smooth muscle (e.g., Zhang et al., 2010) and endothelial cells (e.g., Wang et al., 2002), skeletal muscle (e.g., Zierath et al., 1998), liver (e.g., Yu et al., 2003), kidney (reviewed in: Ruan et al., 2008), and brain (e.g., Sundararajan et al., 2005). This wide expression pattern in various peripheral tissues and brain, coupled with the important role of metabolism and inflammation in aging processes, suggest that PPARγ signaling may influence aging.

3.2 Role of PPARγ in aging

Both human and rodent studies suggest that PPARγ signaling may contribute to aging processes. In genome-wide association studies, for example, PPARγ polymorphisms (particularly of the PPARγ2 isoform) are associated with increased longevity (Barbieri et al., 2004) and in some, but not all studies, with reduced age-related cognitive decline (Johnson et al., 2008; Yaffe et al., 2008). Moreover, PPARγ expression and activity is reduced during aging in rodents, and this may contribute to age-associated loss of function. For instance, aged senescence-accelerated prone mice (SAMP1) have reduced PPARγ mRNA and protein levels in adipose tissue (Haramizu et al., 2011). Similarly, aging decreases PPARγ mRNA and protein expression, as well as DNA binding activity in rat kidney, while caloric restriction (a limited feeding paradigm that delays aging) attenuates this age-related decline (Sung et al., 2004). Finally, reduced PPARγ signaling (by genetic deletion of various PPARγ isoforms from either white adipose tissue or the entire body) results in reduced longevity in mice (Argmann et al., 2009). Taken together, this work suggests that during aging, reductions in PPARγ signaling act to further promote aging processes. It is interesting to speculate that the down-regulation of PPARγ observed in peripheral tissues during aging may also occur in the brain, contributing to aging-associated impairments. Additional research is needed to test this speculation.

Notably, consistent with this idea, treatments that increase PPARγ activity reverse age-related disturbances. For example, treatment of aged rats with a PPARγ activator (2,4-TZD) blunts age-related increases in oxidative stress and inflammatory markers in kidney (Sung et al., 2006). In addition, the PPARγ agonist Rosiglitazone attenuates age-related increases in inflammatory indices in hippocampus, and restores hippocampal synaptic function (e.g., long-term potentiation; LTP) in aged rats (Loane et al., 2009). Notably, PPARγ activators can also upregulate PPARγ expression, thereby preventing age-related decreases in PPARγ levels (Sung et al., 2006). This suggests that treatment with PPARγ agonists could possibly be used to counter the reduced PPARγ activity that otherwise occurs during aging, resulting in the prevention and/or reversal of the effects of aging.

As discussed above, PPARγ activity is modulated by numerous transcriptional co-activator proteins, including PPARγ coactivator 1 (PGC-1; Corton and Brown-Borg, 2005). Several

of these co-activators have been strongly implicated in aging processes. For example, PGC-1α and PGC-1β, are thought to contribute to longevity in caloric restriction paradigms (Corton and Brown-Borg, 2005). Perhaps some (or much) of the age-related actions of these co-activators are mediated via their effects on PPARγ activity.

4. Regulation of stress responses by PPARγ

The strong associations among PPARγ, aging, and stress disturbances suggest that PPARγ signaling itself may play a role to regulate stress responses. In fact, stress exposure increases both the expression and activity of PPARγ in brain cortex (Garcia-Bueno et al., 2005; Garcia-Bueno et al., 2008). These elevations in PPARγ expression appear to be mediated by stress-induced increases in glucocorticoids, catecholamines and glutamate neurosignaling (Garcia-Bueno et al., 2008).

In turn, PPARγ signaling blunts acute physiological stress responses, perhaps as a form of endogenous neuroprotection. Our group has reported, for example, that treatment of rats with the PPARγ agonist Rosiglitazone modifies brain neuronal activation by subsequent stress exposure. Specifically, Rosiglitazone decreases restraint stress-induced cfos expression in the PVN and arcuate hypothalamic nucleus (Ryan et al., 2012; Figure 1). Consistent with a previous report that Rosiglitazone reduces the plasma corticosterone response to a forced-swim stress (Eissa Ahmed et al., 2009), we also observed a blunted plasma corticosterone response to restraint stress, without altering the plasma ACTH response (Ryan et al., 2012; Figure 2). The disassociation between plasma ACTH and corticosterone in this study suggests that Rosiglitazone may act, at least in part, by reducing adrenal responsivity to ACTH. This could occur by blunting stress-induced sympathetic drive to the adrenal gland (Ulrich-Lai and Engeland, 2002). Consistent with this possibility, Rosiglitazone treatment reduces the tachycardic response to restraint, likely via reduced sympathetic drive to the heart (Ryan et al., 2012; Figure 2). Taken together, these data suggest that PPARγ signaling can attenuate brain activation of both the HPA axis and sympathetic nervous system during the acute response to stress.

5. Dual role for PPARγ in stress and aging

5.1 PPARγ may represent a critical mechanistic link between stress and aging

Stress and aging have surprisingly similar consequences to brain (Figure 3). Both conditions alter neuronal function and structure (e.g., induce calcium dysregulation and downregulate glucocorticoid receptors), induce neuroinflammation and oxidative stress, and alter neuronal metabolism, which to varying extents have been causally-linked with the development of stress and aging pathology (Blass et al., 1997; Kitraki et al., 1999; Joels et al., 2004; Garcia-Bueno et al., 2005; Sung et al., 2006; Garcia-Bueno et al., 2007; Loane et al., 2009; Mizoguchi et al., 2009). Thus, induction of one or more of these brain disturbances by either stress or aging could predispose for the development of dysfunction in the other. Notably, PPARγ is expressed in brain regions that regulate both stress and aging (e.g., hippocampus; Moreno et al., 2004), and may be able to reduce each of these brain consequences in the face of either stress or aging. For example, PPARγ agonists inhibit major calcium influxes to hippocampal neurons to limit neuronal vulnerability (Pancani et al., 2009). Moreover, PPARγ activation prevents age-related declines in glucocorticoid receptor in the hippocampus (Escribano et al., 2009), which may help to maintain appropriate glucocorticoid negative feedback. PPARγ agonists also prevent both stress- and aging-induced neuroinflammation and oxidative stress (Garcia-Bueno et al., 2005; Sung et al., 2006; Loane et al., 2009). In addition, PPARγ agonists can prevent the metabolic effects of stress, and perhaps aging, although at least some of the metabolic effects of PPARγ agonists appear to be mediated by non-PPARγ mechanisms (Izawa et al., 2009). Lastly, PPARγ

agonist treatment reduces physiological responses to stress (Figures 1 and 2; Ryan et al., 2012), and may thereby limit the contribution of stress to aging-related brain pathology. Collectively, this suggests that PPARγ may be a critical link between brain stress and aging processes, as well as a potential target for therapeutic strategies.

5.2 Implications for aging- and stress-related brain disorders

PPARγ agonists (and modulators) hold therapeutic potential for many age- and stress-related disorders. For instance, Alzheimer's disease is typified by the accumulation of beta-amyloid peptides and neurofibrillary tangles in brain, and is accompanied by inflammation and altered brain metabolism (reviewed in: Jiang et al., 2008). In animal models of Alzheimer's disease, treatment with PPARγ agonists effectively attenuates disease indices, including improving cerebral blood flow, glucose metabolism, and behavioral impairments, while reducing brain inflammation (Jiang et al., 2008; Nicolakakis et al., 2008). Moreover, Rosiglitazone improves memory and cognition in Alzherimer's patients (Jiang et al., 2008), suggesting that PPARγ is positioned to play a role in Alzheimer's disease progression and treatment. Notably, Rosiglitazone normalizes the HPA disturbances that occur in a mouse model of Alzheimer's disease by reversing both glucocorticoid receptor downregulation and elevations in plasma corticosterone levels (Escribano et al., 2009), suggesting that the therapeutic actions of PPARγ may occur, at least in part, via reducing HPA axis overactivity. Furthermore, reductions in neuroinflammation by PPARγ agonists may make them useful for the treatment of stroke. For instance, Pioglitazone suppresses the NF-kappaB apoptotic signaling pathway via activation of PPARγ, leading to improved recovery (i.e., reduced infarct size) after cerebral artery occlusion (Zhang et al., 2011).

Lastly, depression is a stress-related psychiatric disorder that often occurs in the elderly, particularly in individuals with chronic diseases that are typical for this age group (e.g., heart failure, arthritis, etc.; Chapman and Perry, 2008). PPARγ agonists reduce indices of depressive-like behavior in animal models , and these effects are blocked by a PPARγ antagonist (Rosa et al., 2008). Moreover, PPARγ polymorphisms are associated with a decreased prevalence of depression (Ji-Rong et al., 2009). Collectively, this work suggests that PPARγ is a promising potential therapeutic target for a multitude of stress- and age-related disorders.

6. Summary

Stress and aging have complex interactions, with stress generally promoting aging processes, and aging often contributing to stress dysregulation. Stress and aging have similar effects on brain, for instance altered neuronal activity, increased neuroinflammation and oxidative stress, and metabolic disturbances. PPARγ regulates all of these aspects of brain function, is altered during stress and aging processes, and also reduces physiological responses to stress, suggesting that it may be a key mechanistic link between stress and aging that holds potential for therapeutic benefit.

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Abbreviations

PPARγ	peroxisome proliferator-activated receptor γ
HPA	hypothalamic-pituitary-adrenocortical

PVN	paraventricular nucleus of the hypothalamus
CRH	corticotropin releasing hormone
ACTH	adrenocorticotropic hormone
RXR	retinoid x receptor
TZD	thiazolidinedione
SAMP1	senescence-accelerated prone mice
LTP	long-term potentiation
PGC-1	PPARγ coactivator 1

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Highlights

- Complex interactions link psychological stress and aging
- Stress and aging have similar effects on brain
- PPARγ can act to prevent the consequences of aging and stress on the brain
- PPARγ agonists also reduce the physiological stress response itself
- PPARγ may represent a critical mechanistic link between brain aging and stress

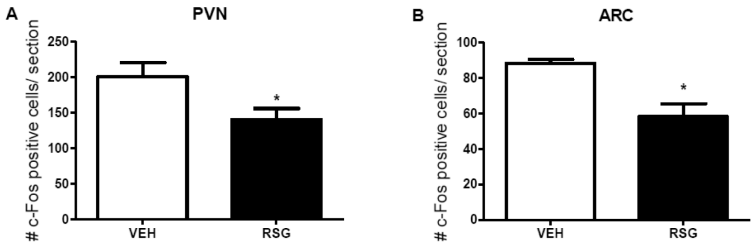

Figure 1.

Acute Rosiglitazone (RSG) treatment reduces the c-Fos response to stress in the PVN and arcuate hypothalamic nucleus. The number of c-Fos-positive cells activated by a 30-min restraint stress is reduced in the PVN (A) and arcuate hypothalamic nucleus (B) of rats given prior oral Rosiglitazone treatment (10 mg/kg body weight per day for 5 d). *$p<0.05$ vs. vehicle (Veh). Reprinted with permission from (Ryan et al., 2012). *Copyright 2012, The Endocrine Society*.

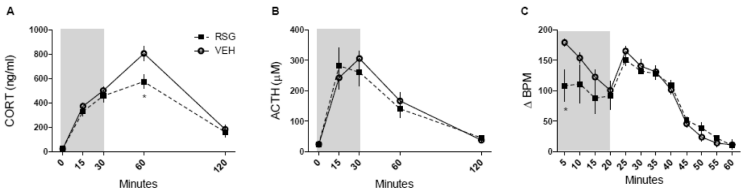

Figure 2.

Acute Rosiglitazone (RSG) treatment reduces physiological responses to stress. Plasma corticosterone (A), plasma ACTH (B), and heart rate (C) responses to restraint stress in rats given prior oral Rosiglitazone treatment (10 mg/kg body weight per day for 5 d). *p<0.05 vs. vehicle (Veh). Reprinted with permission from (Ryan et al., 2012). *Copyright 2012, The Endocrine Society*.

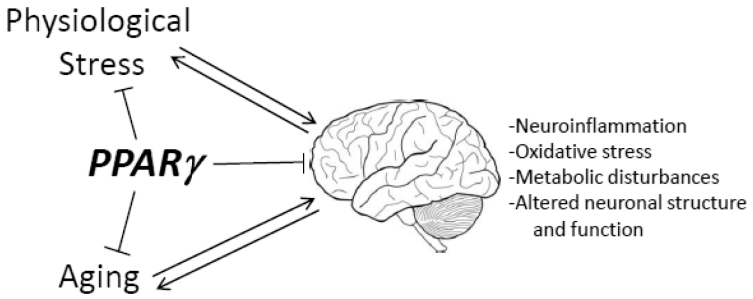

Figure 3.

PPARγ is a potential mechanistic link between stress and brain aging. Brain aging and physiological stress induce similar changes in brain, including altered neuronal function, increased neuroinflammation and oxidative stress, and metabolic dysregulation. These brain disturbances have been implicated in the development of stress and aging pathology, suggesting that stress may promote vulnerability to brain aging by inducing one or more of these disturbances and vice versa. PPARγ can normalize brain function and metabolism and reduce neuroinflammation and oxidative stress. Notably, PPARγ can also act to reduce physiological responses to stress, thereby mitigating the effects of stress and aging on brain. Taken together, this suggests that PPARγ may represent a useful therapeutic target for stress- and age-related disorders. Arrowhead denotes promotion of effects, blunt line denotes inhibition of effects.