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Astrocyte plasticity induced by emotional stress: A new partner in psychiatric physiopathology?

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ABSTRACT

A growing body of evidence has demonstrated that astrocytes play a pivotal role in the normal functioning of the nervous system. This new conceptual framework has set the groundwork to be able to hypothesize that astrocytes could underlie signs and symptoms of mental diseases. Stress is a major risk factor in the etiology of several psychiatric diseases, such as anxiety disorders and depression. Hence, understanding the effects of stress on astrocytes and how these changes contribute to the development of psychiatric endophenotypes is crucial for both a better comprehension of mental illness and for potential targeted treatment of stress-related mental disorders. Here, we describe the currently used approaches and recent evidence showing astrocyte alterations induced by chronic and acute stress in animals. In addition, the relevance of these changes in stress-induced behavioral sequelae and human data linking astrocytes with neuropsychiatric disorders related to stress are also discussed. All together, the data indicate that astrocytes are also an important target of stress, with both chronic and acute stressors being able to alter the morphology or the expression of several astrocyte specific proteins in brain areas that are known to play a critical role in emotional processing, such as the prefrontal cortex, hippocampus and amygdala. Furthermore, different lines of evidences suggest that these changes may contribute, at less in part, to the behavioral consequences of stress.

1. Introduction

Stress is an adaptative physiological response that prepares the organism to face events that represent a physical and/or psychological threat. Hence, it is essential for survival and dealing with situations that require rapid "flight or fight" responses. However, when the stressors are overwhelming or are repeated over time they can eventually lead to a pathology, especially when the predictability, control and coping mechanisms are perceived as being insufficient to deal with the demands placed on them (Franklin et al., 2012; Koolhaas et al., 2011; McEwen and Gianaros, 2010). In fact, stress is considered to be one of the main risk factors for the development of psychiatric disorders such as anxiety-related disorders, depression and drug addiction (Edwards et al., 2013; Guimaraes et al., 2006; Papp et al., 2014; Shin and Liberzon, 2010). In general, brief and intensive aversive situations can provoke symptoms of anxiety (Bazak et al., 2009; Bignante et al., 2010), while chronic mild stress tends to induce a more depression-related phenotype (Elizalde et al., 2010; Zhu et al., 2014). Therefore, the comprehension of the neurobiological changes induced by stress and their functional consequences is crucial for achieving a realistic understanding of these psychiatric illnesses, which are highly disabling and lead to hefty economic costs (Franklin et al., 2012; McEwen and Gianaros, 2010; Popoli et al., 2011).

Stress is a relevant issue in neuroscience and has been the subject of intense research over many decades. A wide body of evidence has shown that the neurotransmitters, neuromodulators and hormones released during stress exposure reshape the brain in the long term. For instance, acute and/or chronic stress alters the morphology of neurons, leading to changes in the spine density and the dendritic length and complexity (Christoffel et al., 2011; Davidson and McEwen, 2012; Giachero et al., 2013). These changes induced by stress can help explain the development of pathologic endophenotypes. For example, stress promotes an increase of dendritic spines in the amygdala (which is a brain region of particular interest for emotional processing) associated with increased anxiety-like behavior (Mitra et al., 2005). Hence, prior stress exposure makes the amygdala more responsive, producing the emotional hyper-reactivity that is a hallmark of anxiety disorders (Martijena and Molina, 2012; Rodriguez Manzanares et al., 2005).

Surprisingly, even though glial cells constitute about 50% of brain cells (Herculano-Houzel, 2014), most of the research on the neurobiology of stress has been focused exclusively on neurons. This bias was

Abbreviations: AQP4, aquaporin 4; ATP, adenosine triphosphate; CUS, chronic unpredictable stress; Cx43, connexin 43; FGF2, astrocytic fibroblast growth factor; GABA, gamma aminobutyric acid; GFAP, glial fibrillary acidic protein; GLAST, glutamate aspartate transporter also known as excitatory amino acid transporter 1 (EAAT1); GLT-1, glutamate transporter-1 also known as excitatory amino acid transporter 2 (EAAT2); GS, glutamine synthetase; S100β, calcium-binding protein β.

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presumably generated by the misconception that glial cells were merely supportive cells, even though this concept has been completely revised since the birth of the tripartite synapse more than two decades ago (Araque et al., 1999). However, there are still remarkably few publications on the effect of stress on astrocytes and even less research on other types of glial cells (for reviews about stress and microglia see Walker et al., 2013; Delpech et al., 2015; and stress and oligodendrocytes see Edgar and Sibille, 2012).

In this review, we will first describe briefly the astrocyte anatomy and function, which lays the groundwork for understanding the multiple ways that make astrocytes an obvious candidate for the alterations in brain functioning that may underlie stress-related pathologies (for extensive reviews about the astrocyte function see: Kimelberg, 2010; Sofroniew and Vinters, 2010; Barres, 2008; Haydon and Nedergaard, 2014). Then, we will summarize the current evidence of the astrocyte alterations induced by stress. Here, we pay particular attention to those studies which used protocols to induce stress, rather than other research that probably caused stress in animals as a collateral effect (e.g. food deprivation, pain, learning, sleep deprivation). We also focus on publications that reported experiments on mature animals, since the developing brain is phenomenologically and mechanistically different to that of an adult one (Kimelberg, 2010). Finally, we analyze if changes in astrocytes could be related to behavioral effects induced by stress. In other words, we attempt to answer the following questions: 1) What do astrocytes do? 2) What effects does stress have on astrocytes? 3) What are the possible functional implications of astrocyte alterations induced by stress? The answer to these questions will give a better insight into how stress interacts with a crucial component of the tripartite synapse.

1.1. Astrocytes are crucial players in synapses

The two main subtypes of astrocytes are the protoplasmic and fibrous ones. Protoplasmic astrocytes are found throughout all gray matter, and exhibit several stem branches that give rise to many finely branching processes. In contrast, fibrous astrocytes are found in white matter and exhibit many long fiber-like processes. The fine processes of protoplasmic astrocytes envelop synapses whereas the processes of fibrous astrocytes contact nodes of Ranvier, with both types of astrocytes forming gap junctions between the distal processes of neighboring astrocytes (Middeldorp and Hol, 2011; Sofroniew and Vinters, 2010). From studies performed on rodent hippocampus and cortex, many finely branching processes from a single astrocyte are estimated to contact several hundred dendrites from multiple neurons and to envelope 100,000 or more synapses (Halassa et al., 2007; Ogata and Kosaka, 2002). The main stem processes of astrocytes, which have glial fibrillary acidic protein (GFAP) as their main constituent, represent around 15% of the total astrocyte volume. These processes ramify progressively to finally generate a dense matrix of thin elaborate terminal processes that associate with neuropil elements and particularly with the synapses. These fine astrocytic processes account for 70–80% of the astrocytic plasma membrane and are devoid of GFAP. It is important to point out that even though perisynaptic processes are found in all brain regions, the proportion of synapses having these and the level of synaptic coverage varies significantly between areas and within the same area (Bernardinelli et al., 2014).

A striking fact is that human protoplasmic astrocytes were found to be 2.6 times larger, and more complex (103 more primary processes) than rodent astrocytes. In addition, their larger diameter and more numerous processes imply that human protoplasmic astrocytes occupy a 16.5-fold greater volume than their mouse counterparts and cover up to 2 million synapses (Oberheim et al., 2009). In an interesting experiment, mice were engrafted with human glial progenitor cells, and upon maturation the recipient brains exhibited large numbers of human astrocytes. The engrafted human glia were gap-junction-coupled to host astroglia, yet retained the size and pleomorphism of hominid astroglia. Notably, the human glial chimeric mice showed enhanced learning and long term potentiation, an effect attributed to an increase in glia released gliotransmiter (Han et al., 2013).

The knowledge about the pivotal role that astrocytes play as fundamental units of the synaptic function began more than two decades ago. This revaluation started with the tripartite synapse concept, which incorporated the astrocytes as the third functional component of the synapse to the classic pre- and postsynaptic elements. This conceptual framework is based on the following aspects (Barres, 2008; Kimelberg, 2010, Perea and Araque, 2010). First, astrocytes control the synaptic microenvironment through transporters, channels and enzymes, with several of these highly or exclusively expressed by these glial cells. For instance, GLAST (glutamate aspartate transporter also known as EAAT1) and GLT-1 (glutamate transporter-1 also known as EAAT2), which remove extracellular glutamate. Furthermore, glutamine synthetase (GS), an enzyme that converts glutamate to glutamine is the precursor to synthetase glutamate and gamma aminobutyric acid (GABA). Second, astrocytes respond to the neurotransmitters released by neurons through membrane receptors, and in fact, most of the receptors present in neurons are also present in astrocytes. Third, they release substances termed "gliotransmiters", which in turn can affect neuronal activity. Overall, they have been shown to be capable of releasing glutamate, D-serine, adenosine triphosphate (ATP), adenosine, GABA, tumor necrosis factor alpha, prostaglandins, atrial natriuretic peptide and brain-derived neurotropic factor, among other candidates.

Astrocytes communicate with each other through calcium waves which are believed to represent for astrocytes what action potentials do for neurons (Perea and Araque, 2010). These calcium signals are mainly due to the release of internal stores by activation of inositol triphosphate receptors, and the calcium waves propagate to neighboring astrocytes through gap junctions, where connexin 43 (Cx43) is an important constituent of the channels. These waves can be observed in vivo by two photon microscopy after different sensory stimulations after 3–10 s, but even faster responses have also been reported. Calcium waves are implicated in gliotransmitter release and probably play an important role in other astrocyte functions. Whole cell patch clamp combined with selective activation of astrocytes has shown that calcium waves can trigger an increase in the excitatory or inhibitory postsynaptic potential frequencies and, in more selected cases, also increase the amplitudes of excitatory potentials. These are transient effects that occur 20–60 s after stimulation (Haydon and Nedergaard, 2014; Perea and Araque, 2010).

An important issue is whether astrocytes can express receptors for stress related hormones and neurotransmitters (e.g. glucocorticoids, norepinephrine) that allow them to directly respond to stress chemical mediators. It has been long established in astrocyte cultures that they produce a morphological change (observed in vitro and called stellation) in response to beta receptor stimulation (Rodnight and Gottfried, 2013). Immunohistochemical studies have shown that beta adrenergic receptors are extensively present in the lateral amygdala astrocytes (Farb et al., 2010) and alpha receptors in the prefrontal cortex (Aoki et al., 1998). In an in vivo study performed on awake rats, stimulation of the noradrenergic locus coeruleus produced astrocyte calcium waves in the frontal or parietal cortex. These astrocyte responses were suppressed by neurotoxic deletion of the locus coeruleus and by the cortical administration of adrenergic receptor antagonists (Ding et al., 2013). In addition, it is known that glucocorticoid and mineralcorticoid receptors are widely expressed in astrocytes and other glial cells (Bohn et al., 1991; Cintra et al., 1994). Moreover, recent postmortem studies in human tissue revealed the presence of glucocorticoid receptors in amygdala (Wang et al., 2014), hippocampus and cortex (Wang et al., 2013). Interestingly, experiments in vitro have demonstrated that corticosterone, at stress relevant concentrations of 0.1–1 μM (Komatsuzaki et al., 2012), induces an increase in the velocity of calcium waves and in gliotransmitter release (Chatterjee and Sikdar, 2013). Taken together,

these findings indicate that astrocytes can directly sense and eventually change their morphology or functionality in response to chemicals released during the stress response.

1.1.1. Astrocyte plasticity

Plasticity is defined as the general capacity of the brain to adapt functionally or structurally to a change in demands (Lucassen et al., 2014). Therefore, astrocytes morphological changes as well as alterations in astrocyte specific proteins in response to a stimulus (e.g. stress) are examples of astrocyte plasticity. In vitro evidence has clearly shown that astrocyte morphology is very dynamic, with highly motile astrocytic filopodia-like processes moving or growing over a time course of only a few minutes or even in seconds (Bernardinelli et al., 2014; Reichenbach et al., 2010). Using organotypic hippocampal slices, a preparation that retains the three-dimensional architecture of astrocyte-synapse interactions, it has been demonstrated that astrocytes can rapidly extend and retract fine processes to engage or disengage postsynaptic dendritic spines (Haber et al., 2006). Studies on intact brain also indicate that mature astrocytes are able to elongate or retract their perisynaptic processes and also alter the whole shape of these cells (Bernardinelli et al., 2014; Rodnight and Gottfried, 2013; Saab et al., 2012). One of the pioneering examples of astrocyte structural plasticity was shown in the paraventricular nucleus of the hypothalamus, which regulates the release of oxytocin, a hormone necessary for milk ejection from mammary glands. During lactation, astrocyte perisynaptic processes retract from the synapses with the consequence (among other coordinated mechanisms) that astrocytes decrease the removal of glutamate from the synaptic cleft, thereby increasing the action of the neurotransmitter. At the time of weaning, the astrocytes then elongate again into the synapses and the oxytocin release returns to normal levels (Theodosis et al., 2008).

1.2. Stress induces astrocyte plasticity

Taking into account that morphological change in neurons is a hallmark of chronic stress effects with resulting increases or reductions (depending of the brain structure) in both dendrite branches and spine density (Christoffel et al., 2011), it could be expected that astrocyte, which are in a close relationship at the synaptic level, could show structural plasticity. However, the complexity of the astrocyte structures and the thickness of the perisynaptic processes have precluded an extensive morphological analysis of the intact brain after stress using the most common microscopy setups. In recent years, several options have been developed such as targeted expression of green fluorescent proteins under the promoter of astrocyte-specific genes or the development of selective dyes (Appaix et al., 2012; Nimmerjahn and Helmchen, 2012). But even in those situations, it is necessary that the expression of the tag occurs in scattered cells, otherwise the overlap in the branches prevents any detailed analysis in single cells. Advances in electron microscopy techniques now allow 3D reconstruction of synapsis, and as a result, very fine analysis can be performed. However, as far as we are aware, it has not been used yet in stress paradigms. Hence, most that we know about stress induced morphological plasticity came from investigations that have used the gold standard marker of astrocyte GFAP detected by immunohistochemistry.

GFAP is an intermediate filament protein present in the astrocyte cytoskeleton, but only expressed in the main processes, hence it does not stain the perisynaptic processes that emanate from the principal astrocyte branches. In addition, changes in GFAP probably not only reflect a structural, but also a functional consequence for the astrocyte physiology, since this protein has been implicated in cell to cell communication, anchoring of proteins and the reaction to brain insults (Middeldorp and Hol, 2011). For instance, cells lacking GFAP proteins do not develop perisynaptic processes with neurons (Weinstein et al., 1991) and have a reduction in the trafficking of the astrocytic glutamate transporter GLAST (Hughes et al., 2004).

An operative distinction between the different stress paradigms that has been shown to be useful for descriptive purposes is whether they are acute or chronic, since this variable may induce different consequences. For example, morphological changes in dendrites are usually more associated with chronic stress rather than with acute exposure (Arnsten, 2009).

1.2.1. Chronic stress

One of the pioneering studies that revealed astrocyte changes induced by stress was performed by Czéh et al. (2006). In this study, adult male tree shrews were subjected to 5 weeks of psychosocial stress, and the number of cells (measured using stereological methods) showed a 25% reduction in GFAP positive cells in the hippocampus. Unfortunately, there was no discrimination of the subareas of hippocampal formation, so one must assume that were no layer-specific effects. Moreover, this work showed that the somatic volume of astrocytes was reduced by 25% in stressed animals. Even though GFAP is not a good marker for somas since it is a protein exclusively present in the main processes, the changes reported are suggestive of an astrocyte process rearrangement. In support of this hypothesis, a recent work carried out an extensive analysis of GFAP staining after chronic restraint described that stress induces a reduction in both the number and shortening of main processes (Tynan et al., 2013).

In another seminal work performed by Banasr and Duman (2008), chronic unpredictable stress (CUS) induced a 19% reduction in the number of GFAP positive cells in the rat infralimbic cortex. These types of observations have been replicated and extended in a number of studies in rats, resulting in one of the most consistently reproducible results in the field (L.F. Li et al., 2013; Liu et al., 2009, 2011; Sun et al., 2012; Tynan et al., 2013; Ye et al., 2011). However, since GFAP is not present in all astrocytes, these studies are not conclusive. Another important limitation of these pioneering works was the lack of measurement of the total cell number with other markers. Hence, it was unclear if there were fewer GFAP positive cells because they had died or maybe had stopped producing GFAP at detectable levels for immunohistochemistry.

Subsequent findings by Gosselin et al. (2009) represented an important step forward in this issue. This research analyzed some broader areas in Wistar Kyoto rats, which are more responsive to stressors and manifest more anxiety and depressive-like behavior compared to Sprague Dawley rats. In this model, GFAP positive cells were again found to be reduced in hippocampus, prefrontal cortex and in amygdala, but not in the other cortical areas evaluated. However, when astrocytes were counted using calcium-binding protein β (s100β) marker which stains astrocyte somas, no differences were observed, suggesting that the astrocytes were not degenerating, but instead that the expression of GFAP was being downregulated. In fact, when the protein level was assessed by western blot, GFAP were found to be decreased in the prefrontal cortex and amygdala. In addition, since there were no differences between strain rats in terms of the number of nuclei quantified with DAPI (which stain all cell types) or with the neuronal marker NeuN, then this strongly suggests that there was no loss of astrocytic cells (or neurons).

Unfortunately, we do not know if the differences reported in Wistar Kyoto rats were acquired during the early stages of development, therefore this model is significantly different from the previous stress chronic paradigms applied to mature animals. However, similar results were obtained with the chronic restraint stress model using a similar staining approach in the prefrontal cortex (Tynan et al., 2013). Regardless of the limitation that Nissl staining was used to identify astrocytes, Kassem et al. (2013) also did not find any differences in the astrocyte number in CA1, amygdala, or retrosplenial cortex after chronic restraint. On the other hand, using the CUS model, a decrease in the GFAP level was reported in the hippocampus detected by western blot (Araya-Callís et al., 2012; Liu et al., 2009) and also at the RNA level in the hippocampus (L.F. Li et al., 2013; Liu et al., 2009) and prefrontal cortex (Banasr

et al., 2010; L.F. Li et al., 2013), indicating that downregulation operates at the transcription level.

A quite different result has been reported by other authors who used the chronic restraint model, in which they found an increase of GFAP positive cells and protein level in hippocampus (Jang et al., 2008; Kwon et al., 2008). Using this model, but analyzing other areas, a GFAP downregulation in the periaqueductal gray and the raphe nucleus was reported (Imbe et al., 2012, 2013). Thus, unlike the CUS and psychosocial stress paradigms, the chronic restraint model has produced more variability in the results of GFAP measurements, with differences in the predictability and controllability in those models probably accounting for the differences reported following stress exposure (Koolhaas et al., 2011).

Another marker of astrocytes that has been studied is s100β. This is a protein that acts as a calcium sensor, which when activated, interacts with several other proteins and thus affects broad cellular functions. Moreover, it is secreted and induces cellular activities by acting in autocrine, paracrine and endocrine manners (Donato et al., 2009). As mentioned above, although the number of astrocytes expressing this protein does not change after stress, the level of s100β has been reported to be increased in the prefrontal cortex (Tynan et al., 2013) and the hippocampus after CUS (Ye et al., 2011; however see Rong et al., 2010). This implies that calcium waves may be altered by stress, but as far as we are aware there are no publications that have measured calcium waves after stress protocols.

As mentioned above, an important aspect of astrocytes is that they are highly interconnected through gap junctions which are the substrate for calcium wave propagation. Accordingly, some authors explored whether the substrate for this communication is disrupted after CUS, and found that the intra-infralimbic diffusion of a permeable dye, which was preferentially spreading among astrocytes through gap junctions, was notably decreased after CUS. Furthermore, alterations in astrocyte gap junctions were confirmed at electron microscopy level and were associated with downregulation of Cx43 (Sun et al., 2012).

A more direct functional measurement of astrocytes after CUS was performed based on infusion of [2–13C]acetate, which has been shown to be preferentially metabolized in astrocytes. The findings of this experiment showed that after stress, the animals had a reduction in the marked glutamate, glutamine and GABA, indicating a slowing in the astrocyte metabolism (Banasr et al., 2010). In the same series of experiments, other proteins that are involved in glutamatergic transmission and preferentially expressed by astrocytes, such as GLT-1, GLAST or GS, were found to be unchanged in the prefrontal cortex after CUS, at least at the mRNA level (Banasr et al., 2010).

A summary of these data is provided in Table 1 and the supplementary comprehensive table.

1.2.2. Acute stress

There was no change in GFAP immunostaining in the hippocampus from rats that were restrained for 2 h with the additional stress of being submerged in water (Sugama et al., 2011). Investigations that observed a downregulation of GFAP in the periaqueductal gray and raphe nucleus in the chronic restraint model did not observe these changes during a shorter stress session (3d/ 6 h compared to the standard 21d/ 6 h), suggesting that changes in GFAP require exposure to the chronic stress protocol (Imbe et al., 2012, 2013). However, when a presumably "stronger stressor" was used (the combination of restrain, forced swimming test and ether exposure in an acute sequential session), there was a reduction of hippocampal GFAP expression in the hippocampus (Xia et al., 2013).

In a predator paradigm in which rats were exposed for 5 min to the sight and smell of a cat, the s100β content was enhanced in cerebrospinal fluid, but not in the hippocampus or cerebral cortex, 1 h after the stressful experience (Margis et al., 2004). A similar result was found in the restraint model (Scaccianoce et al., 2004), suggesting that s100β is rapidly released from astrocytes after acute stress. Other experiments have further shown an increase in the number of astrocytes expressing the inflammatory protein interleukin 1β in the hippocampus, hypothalamus, amygdala, and periaqueductal gray (Sugama et al., 2011). In addition, 3 h of restraint induced an increase of astrocytic fibroblast growth factor (FGF2) which was associated with an enhancement in hippocampal neurogenesis, suggesting a beneficial effect of astrocyte release FGF2 induced by stress (Kirby et al., 2013).

Table 1
Chronic stress effects on Astrocyte related proteins.

	Stress Protocol	Astrocyte Related Proteins						
Reference	Chronic	GFAP	s100β	GLT-1	GLAST	GS	Brain area	Prevention (*a*)
Cze'h et al. (2006)	Social defeat (5 weeks)	↓					Hipp	Yes
Jang et al. (2008)	REST	↑= (*b*)					Hipp, Ctx, ST, Cerebel	Not tested
Banasr and Duman (2008)	CUS	↓					PL	Not tested
Liu et al. (2009)	CUS	↓					Hipp	Yes
Gosselin et al. (2009)	Strain (*c*)	↓	=↓ (*d*)				PFC, BLA, Hipp	Not tested
Banasr et al. (2010)	CUS	↓		=	=	=	PFC	Yes
Rong et al. (2010)	CUS		↓				Hipp	Yes
Liu et al. (2011)	CUS	↓					Hipp	Yes
Ye et al. (2011)	CUS	↓	↑				Hipp	Yes
Araya-Callis et al. (2012)	Social defeat (4 weeks)	↓					Hipp	No
Imbe et al. (2012)	REST	↓		↓			PAG	Not tested
Sun et al. (2012)	CUS	↓					PL	Yes
Imbe et al. (2013)	REST	↓	=				RVM	Not tested
Tynan et al. (2013)	REST	↓	=↑ (*e*)				PFC	Not tested
L.F. Li et al. (2013)	CUS	↓					PFC	Yes

↑: higher, ↓: lower, = : no differences, in the level of protein\transcript in the stress group compared to control.
a) Effect was prevented by an antidepressant drug or another putative protective treatment.
b) Increases were seen in Hipp and Ctx, non changes were seen in ST and Cerebel.
c) Wistar-Kyoto rats which is a strain more vulnerable to stress than Sprague-Dawley were compared without applying any stress protocol.
d) Equal in the number of stained cells but higher in the levels measured by western blot in Wistar-Kyoto rats.
e) Equal in the number of stained cells and in the intensity of staining in the somas but higher in extrasomal areas.
Brain areas: BLA: basolateral amígdala, Cerebel: cerebellum, Hipp: hipocampo, PAG: periaqueductal gray, PFC: prefrontal cortex, PL: prelimbic cortex, RVM: rostral ventromedial medulla, ST: striatum. Proteins: GFAP: Glial fibrillary acidic protein, GLAST: glutamate aspartate trasporter, GLT-1: glutamate transoporter-1, GS: glutamine, S100β: calcium-binding protein β. Stress model: CUS: chronic unpredictable stress (some authors called this chronic mild stress), REST: restraint.

An interesting approach to carry out an extensive screening of astrocyte changes triggered by stress is by using the microarray, which allows hundreds of transcripts to be measured, then with the assistance of bioinformatic tools, it is possible to link in clusters that belong to astrocyte proteins. This method has in fact been used in lateral/basolateral amygdala samples from rats subjected to 15 footshocks over a 93 minute period (Ponomarev et al., 2010). Interestingly, many astrocyte enriched genes were either upregulated or downregulated in the stressed animals, and these seemed to be long lasting changes since measurements were taken 22 days after stress. For example, an upregulation of GLAST and downregulation of serine racemase, which synthetizes the gliotransmiter D-serine, were detected in stressed animals.

Taken together, these data indicate that acute stress is able to induce changes in astrocytes, which suggests that these cells are rapidly sensing and responding to hormones and/or neurotransmitter released during the stress response. Furthermore those changes could be long lasting. However, an issue not answered in most publications cited above, either after acute or chronic paradigms, is whether these astrocyte changes are reversible after a time of recovery. This is important, since more permanent changes are most probably related to the physiopathological changes that underlie long-lasting maladaptive behavioral effects of stress, such as anxiety and depression.

A summary of these data is provided in Table 2 and the supplementary comprehensive table.

1.3. Does stress induced astrocyte plasticity play any role in the behavioral sequelae induced by stress?

Many studies have suggested that chronic and acute stress under certain experimental conditions can induce depressive and anxiety-like behavior in animals (Guimaraes et al., 2006; Zurita et al., 2000). For instance, the CUS model induces anhedonic like effects, operationally defined as a decrement in sucrose consumption, and also hopelessness measured by forced swimming test and active avoidance paradigms (Banasr et al., 2010; Cao et al., 2013). On the other hand, as described in this review, there is extensive evidence that chronic and acute stress are capable of inducing changes in astrocyte morphology or functionality, which are presumed to be deleterious for brain functioning and eventually form a part of the physiopathology of stress related disorders. Therefore, it is important to consider the role that astrocyte induced plasticity may be playing in the behavioral sequelae of stress.

Several of the studies presented above using stress chronic models have also shown that antidepressant drugs, e.g. fluoxetine and clomipramine, which prevented stress-induced astrocyte changes were able to normalize stress-induced behavioral changes (Czéh et al., 2006; Liu et al., 2009; Sun et al., 2012; see the supplementary comprehensive table for a summary of those works that reported a prevention on astrocyte effects induced by stress). This strongly suggests that astrocytes are involved in the behavioral consequences of stress. The question about their sufficiency, however, is not simple to address, but the use of gliotoxins and transgenic animals has indicated that astrocytes may indeed play a causal role in the long lasting effects induced by stressful experiences. One of the first experimental findings supporting this proposal came from experiments performed by Banasr and Duman (2008). By applying L-alpha-aminoadipic acid microinjections into the rat prefrontal cortex, which selectively decreased the number of GFAP positive cells by 23% (but not neurons), anhedonia and hopelessness were induced in the short term. This type of experiment has been subsequently replicated and extended using other gliotoxins (Domin et al., 2014; John et al., 2012; Lee et al., 2013; Sun et al., 2012). Moreover, gliotoxin-induced depressive behavior was prevented by systemic antidepressant drugs (Domin et al., 2014).

Transgenic mice with an alteration in the nitric oxide synthetase 2 (which is predominantly expressed in glial cells) produce high levels of nitric oxide in astrocyte. This astrocytic alteration render the animals more susceptible to acute stress as evidenced by higher anxiety-like behavior, increased acoustic startle responses, and higher plasma corticosterone levels compared to wild type mice after predator scent exposure (Abu-Ghanem et al., 2008). Another mice which had a reduction in the ATP secreted from astrocytes showed a depressive phenotype, which was similar to the one observed after chronic stress paradigms (Cao et al., 2013), Furthermore, other transgenic line, in which the release of ATP from astrocytes was increased after injection of a specific ligand, induced antidepressant-like effects in the forced swimming test and in the chronic social defeat stress model (Cao et al., 2013). Thus, selective alterations of the astrocyte machinery were sufficient to either trigger stress-like effects or give protection from the behavioral consequences of stress. However, these findings have been challenged by a recent paper which did not find any behavioral alteration in several emotional and cognitive tasks in transgenic mice that were knockout for astrocytic IP3R2 (inositol triphosphate

Table 2
Sub-chronic and acute stress effects on astrocyte related proteins.

	Stress Protocol	Astrocyte Related Proteins						
Reference	Sub-chronic	GFAP	s100β	GLT-1	GLAST	GS	Brain area/tissue	Prevention (*a*)
Kwon et al. (2008)	REST 4 days (2 h/day)	↑= (*b*)					CA1, ST, PVN	
Imbe et al. (2012)	REST 3 days (6 h/day)	=		=			PAG	Not tested
Imbe et al. (2013)	REST 3 days (6 h/day)	=↓ (*c*)	=	=			RVM	Not tested
	Acute							
Scaccianoce et al. (2004)	REST (2 h)		↑				Blood	Not tested
Margis et al. (2004)	PREDATOR		=↓↑ (*d*)				Hipp, Ctx, CSF	Not tested
Ponomarev et al. (2010) (*e*)	SHOCK				↑		BLA\LA	Not tested
Sugama et al. (2011)	REST (2 h)	=					Hipp, Hyp, Amy, PAG	Not tested
Xia et al. (2013)	SPS	↓					Hipp	Yes

↑: higher, ↓: lower, = : no differences, in the level of protein\transcript in the stress group compared to control.
a) Effect was prevented by an antidepressant drug or another putative protective treatment.
b) Increases were seen in CA1 and ST, non changes were seen in PVN.
c) Reduction was detected in the RVM with western blot but there were no differences when immunohistochemistry was used in the Raphe Nucleus, a part of the RVM.
d) Increases were seen in CSF at 1 hour after stress and a reduction at 24 hours after stress. Non changes were seen in Hipp and Ctx.
e) Several others astrocyte (and neuronal) genes were found altered in this study by stress, here we report the most relevant for this review.
Brain areas/tissue: Amy: amígdala, BLA\LA: basolateral\lateral amígdala, CA1: cornu ammonis 1 (subfield of Hipp.), CSF: cerebrospinal fluid, Ctx: cerebral cortex, Hipp: hipocampo, Hyp: hypothalamus, PAG: periaqueductal gray, PVN: paraventricular nucleus, RVM: rostral ventromedial medulla, ST: Striatum. Proteins: GFAP: Glial fibrillary acidic protein, GLAST: glutamate aspartate trasporter, GLT-1: glutamate transoporter-1, GS: glutamine, S100β: calcium-binding protein β. Stress model: REST: restraint, SPS: single prolonged stress.

type 2 receptor) which is a critical receptor for triggering calcium wave signals (Petravicz et al., 2014).

Current advances in more selective and less invasive ways of activating or silencing astrocyte activity, such as optogenetic and designer receptors exclusively activated by designer drugs (D. Li et al., 2013), will be critical for understanding how astrocytes contribute to the emergence of the behavioral aberrations associated to stress exposure, as well as their participation in the stress response itself, which to date is a largely unexplored topic (for a recent work showing an autonomic response by selective modulation of astrocytes, see Agulhon et al., 2013).

1.4. Evidence of astrocyte alterations in human psychiatric disorders associated with stress

Research related to this topic is strongly limited by the lack of non-invasive techniques that allow discriminating cell types in the intact brain. As a result, the only direct way of visualizing astrocytes in human brain is through postmortem studies. As far as we know the principal psychiatric illness strongly associated to stress that has been studied in humans and focused on glial cells is depression. Related to this, several cell counting studies have reported decreases in the packing density or number of the Nissl-stained populations of glial cells in subjects diagnosed with major depression, compared to non-psychiatric controls. These types of changes have been observed in fronto-limbic brain regions, including the dorsolateral prefrontal cortex, orbitofrontal cortex, subgenual cortex, anterior cingulate cortex and amygdala (Rajkowska and Stockmeier, 2013). Another approach to study astrocyte morphology has been the Golgi staining method, which allows the identification of scattered cells permitting a 3D reconstruction of the whole individual cell. This technique was applied by Torres-Platas et al. (2011) in the anterior cingulate cortex from suicidal depressive patients, and compared to matched control samples. These authors found an increase in the volume of the cell body and the number and length of the fibrous astrocyte processes located in the white matter adjacent to the anterior cingulate cortex, but not in the cortex itself.

Immunohistochemistry with antibodies against astrocyte specific proteins applied to postmortem tissue enables a more direct assessment of the astrocyte contribution to glial alterations in depressive subjects. Müller et al. (2001) observed a reduction of GFAP immunoreactivity in the hippocampal areas CA1 and CA2, with the caveat that an observational criterion was used, and even in controls these values revealed no or only low immunoreactivity. A lower level of coverage of GFAP staining as well as a reduction in the number of GFAP positive cells in the dorsolateral prefrontal cortex were found in young depressed patients, but not in older patients (Miguel-Hidalgo et al., 2000). Similar findings were obtained in the orbitofrontal cortex using western blot technique and fraction area of immunostaining (Miguel-Hidalgo et al., 2010). In another study which used the s100β marker instead, a decrease in the number of astrocytes was also found in depressed and bipolar patients compared to matched controls (Gos et al., 2013). By studying the amygdala postmortem tissue belonging to different psychiatric patients, another investigation found a reduction in GFAP positive astrocytes, but only in depressive disorder (Altshuler et al., 2010, however, see Hamidi et al., 2004). In contrast, glucocorticoid receptors in amygdala astrocytes were increased in depressive patient compared to healthy controls or bipolar disorder patients (Wang et al., 2014), suggesting that astrocytes are sensing and responding to changes in stress hormone levels.

Other measurements that have been applied to human postmortem tissue include in situ hybridization and quantitative real-time PCR, which allow the detection and quantification of the mRNA present in brain sections and dissected dissolved tissue, respectively. Using this approach in the locus coeruleus (Bernard et al., 2011), it was found that several transcripts for astrocyte proteins were altered in major depression but not in bipolar disorder. Specifically a reduction of GLT-1, GLAST, GS, GFAP, s100β, AQP4 (aquaporin 4, a water channel), Cx43, and connexin 30 (another gap junction protein) was observed. A decrease in the expression of GLT-1, GLAST, and GS mRNAs was also described in the anterior cingulate and dorsolateral prefrontal cortices (Choudary et al., 2005). Correspondingly, some of these transcripts have been also found reduced at the protein expression level in other areas. For instance, Cx43 (Miguel-Hidalgo et al., 2014), AQP4 (Rajkowska et al., 2013), GLT-1, GLAST (Miguel-Hidalgo et al., 2010) were decreased in the orbitofrontal cortex of depressive patients. Glutamate astrocytic transporters were also reduced in the amygdala of alcoholics individuals (Kryger and Wilce, 2010) which, according to these authors, could increase amygdala activity and the expression of associative memories and anxiety which underlie continued drug-seeking and chronic relapse.

Since s100β is secreted into the blood stream, this protein makes it possible to perform serum measurements in living patients allowing to investigate alterations of this astrocyte related protein in different illnesses. Several studies have used this approach in psychiatric populations and a meta-analysis has been performed by Schroeter et al. (2008) indicating that serum levels of s100β are consistently elevated during acute episodes of depression, with an increase respect to control of 2.57 ± 0.70 (mean ± SD) fold. It is important to note that this increase is not specific to depression, as bipolar patients also revealed increases in serum s100β. On the other hand, as100β is also expressed in oligodendrocytes and some other body cells, then the respective contribution of these cells to the blood concentration is uncertain.

A big limitation in almost all human studies with depressive patients cited above is that most of the subjects were under antidepressant or other kind of psychopharmacology treatment that could affect the astrocyte measurement performed. However, some of these studies consider this issue and made statistical comparison between persons under treatment vs no medicated patients. For instance, in the study of Miguel-Hidalgo et al. (2010) when subjects with depression that had antidepressant medication detected in the postmortem toxicology screening were compared to those without antidepressant, no differences in GLT-1, GLAST, GS or GFAP levels were detected. Similarly, no medication effects were observed by Gos et al. (2013), Rajkowska et al. (2013), Wang et al. (2014) and Miguel-Hidalgo et al. (2014). Interestingly, studies involving serum s100β measurement before and after successful treatment with antidepressive drugs indicated that s100β levels (which are larger than in control subjects) were reduced after treatment (Schroeter et al., 2008). Even though the effect was small, this meta-analysis found a significant positive correlation between clinical treatment effects and serological treatment effects of S100β, suggesting that this protein could be a biomarker of depression.

Investigations in non-psychiatric populations presumed to be exposed to robust stressors have also suggested that stress affect astrocytes. In this sense, serum s100β measurements taken two days after cardiac surgery along with Spielberger's anxiety inventory performed in cardiologic patients indicated that individuals with elevated s100β had higher levels of state anxiety and trait anxiety (Bergh et al., 2007). In the same way, s100β, as well as serum cortisol, were significantly increased in soldiers during combat training compared to at rest period being concomitant to a greater stress, anxiety and depression levels assessed by psychological questionnaires (Li et al., 2014).

Taken together, the human data from depressive patients showed a reduction of astrocyte markers in the dorsolateral prefrontal cortex, orbitofrontal cortex, hippocampal CA1 and CA2 and amygdala. Based on the results obtained in animals, it is possible to speculate that these changes might be caused by the effects of being exposed to chronic stress. However, while the animal data indicate that stress induced a down-regulation of astrocyte markers without inducing “astrodegeneration”, human studies have revealed a reduction in the number of the glial

population stained with Nissl or s100β, suggesting that they degenerate or that the proliferation was reduced. Undoubtedly, depression is a multifactorial disease that is not only dependent on stress, and as referred above, there is evidence that reduction of GFAP could be an early manifestation that "disappears" at more advanced stages of the illness. On the other hand, studies on individuals that underwent a significant stress exposure, revealed clear changes in an astrocyte related protein (s100β), which could be detected even at the blood level, suggesting a strong involvement of astrocytes in response to stress. Clearly, more human studies are still necessary to fully understand the impact of stress on astrocytes functioning and the neurobiological and behavioral consequences.

1.5. How astrocyte alterations induced by stress could contribute to pathophysiological changes that underlie behavioral sequelae of stress?

As mentioned before, the retraction of astrocytes from synapses in the hypothalamus has been shown to be critical to increase the glutamate effects as a result of a reduction in the removal of this transmitter, which is mainly taking up by astrocytes transporters (Theodosis et al., 2008). In the same direction, the retraction of astrocytes (Bergmann glia) in cerebellar cortex enhances the excitatory postsynaptic current amplitude of Purkinje cells (Saab et al., 2012). In hippocampus also a mutation that makes astrocytes to retract from the synapses facilitates glutamate spillover and increases the NMDA currents in pyramidal neurons after burst stimulation (Tanaka et al., 2013). On the other hand, acute and chronic stress has been associated with increases in glutamate release/content in the synaptic cleft, and excitotoxicity has been claimed as an important mechanism to produce cellular effect that underlie morphological and behavioral disturbances induced by stress (Popoli et al., 2011). Hence, the reduction in astrocyte processes induced by stress could be a mechanism by which enhancement in excitability or even excitotoxicity is produced or increased. In fact, administration of GLT-1 blocker in PFC induced anhedonic-like behavior in rats (John et al., 2012) and systemic injection of rulizole, a drug that facilitates glial cell glutamate uptake and decreases presynaptic release, prevented both the behavioral and astrocyte sequelae of chronic stress (Banasr et al., 2010).

Another way that stress-induced astrocyte alterations could affect behavior is through modulation of the GABAergic system. GABAergic synapses play a pivotal role in both anxiety disorders and emotional disturbance induced by stress (Martijena and Molina, 2012; Rodriguez Manzanares et al., 2005). On the other hand, recent findings suggest that astrocytes release GABA and regulate GABA extrasynaptic content, which in turn is responsible for tonic GABA-A receptor-mediated currents (Yoon and Lee, 2014). Interestingly, chronic stress exposure induced a loss of tonic (but not phasic) inhibition in amygdala, an effect blocked by glucocorticoids synthesis inhibitor and mimicked by corticosterone (Liu et al., 2014). Moreover, a study performed in slices from thalamus has shown that astrocytes also release a peptide that mediates a benzodiazepine-mimicking effect, and treatment with a gliotoxin reduced the effective inhibitory charge of GABA-A mediated spontaneous inhibitory postsynaptic currents (Christian and Huguenard, 2013). Thus the retraction of astrocytes from synapses or impairment in their function after chronic stress could account for the loss of tonic inhibition and consequent excitability of amygdala which is the hallmark of anxiety disorders like posttraumatic stress disorder (Shin and Liberzon, 2010).

1.6. Mechanisms that could underlie stress-induced astrocyte plasticity

The relatively newness of this field of research precludes any systematization of the possible mechanisms of stress induced effects on astrocytes, but since these cells express receptors sensitive to stress hormones and neurotransmitters these are obvious candidates that could trigger downstream cascades that ultimately affect astrocyte morphology and physiology. Indeed, corticosterone administration to rats (5 days or 4 months) caused a reduction in GFAP content in hippocampus and cortex (O'Callaghan et al., 1991) which, as in the chronic stress, it operates at the transcription level (Nichols et al., 1990). Experiments in astrocyte cultures have demonstrated that corticosterone induces an increase in the velocity of calcium waves and the rate of gliotransmitter release, which were dependent on rearrangement of cytoskeletal elements (Chatterjee and Sikdar, 2013). These suggest that stress affects astrocytes directly and their changes are not a secondary response to neurons or other cells.

Norepinephrine is also able to modulate astrocyte activity. Using 2-photon microscopy in mice that express a Ca^{2+} indicator in astrocytes, it was shown that alpha adrenoceptor antagonists inhibited the activation of astrocyte networks that are triggered by the arousal associated to locomotion (Paukert et al., 2014). This effect seems to be specific for norepinephrine since it was abolished by chemical depletion of norepinephrine but not by antagonists of serotonergic, muscarinic, metabotropic glutamatergic, or cannabinoid receptors (Paukert et al., 2014). In the same direction, when the locus coeruleus output was triggered by an air-puff startle response it produced astrocyte calcium waves in prefrontal cortex that were suppressed by cortical administration of alpha adrenergic receptor antagonists or chemical depletion of norepinephrine (Ding et al., 2013). Another way that norepinephrine could affect astrocytes is through phosphorylation of GFAP (Mobley and Combs, 1992) which is believed to regulate the structural plasticity of glial filaments (Takemura et al., 2002). Another interesting in vitro finding indicates that astrocyte activation of noradrenergic β2 receptors induces the release of growth factors (including FGF-2, BDNF, NGF-β and GDNF) that increases neuronal complexity (Day et al., 2014). This could be a mechanism by which stress increases the complexity of dendritic arborization in amygdala which is thought to underlie several behavioral sequelae of stress (Christoffel et al., 2011). In fact, a long tradition in stress research has linked the β2 activation in the stress-induced enhancement in fear learning (McGaugh and Roozendaal, 2002).

2. Conclusions and remarks

Stress effects on neuron morphology and function have been the subject of numerous investigations, which have been crucial for a better understanding of the mechanisms through which stress induces deleterious effects on brain functioning and behavior. As shown in this review, different approaches in animals and humans have indicated that astrocytes are also an important target of stress, with both chronic and acute stressors being able to alter the morphology or the expression of several astrocyte specific proteins in brain areas that are known to play a critical role in emotional processing, such as the prefrontal cortex, hippocampus and amygdala. Furthermore, different lines of evidences have suggested that these changes may underlie the behavioral consequences of stress. First, astrocyte cellular effects induced by stress were prevented by the administration of drugs that averted the behavioral sequelae of stress. Second, astrocyte specific toxins induced similar behaviors to those observed after stress exposure. Third, astrocyte specific alterations in transgenic mice were able to emulate stress effects. Human data from psychiatric populations also support the notion that astrocytes are affected in mental disorders, with there being a remarkable agreement indicating that astrocyte specific proteins are decreased in major depression, an illness strongly associated to stress. All together the data suggest that stress hormones (e.g. glucocorticoids) and neurotransmitters (e.g. norepinephrine) through their receptors located in astrocytes directly induce intracellular cascades that ultimately introduce changes in the morphology/physiology of astrocytes that alters the normal functioning of tripartite synapsis in a pathophysiological direction that is known to drive behavioral sequelae of stress, like increases of glutamate transmission and/or reduction of GABAergic transmission.

A real challenge in the future will be to avoid a new bias by studying the stress effects in astrocytes without considering the interplay with neurons and other cells, which interact among themselves and with the other body systems to determine the health of an organism.

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Appendix A. Supplementary data

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