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Effects of chronic stress on the auditory system and fear learning: an evolutionary approach

Abstract: Stress is a complex biological reaction common to all living organisms that allows them to adapt to their environments. Chronic stress alters the dendritic architecture and function of the limbic brain areas that affect memory, learning, and emotional processing. This review summarizes our research about chronic stress effects on the auditory system, providing the details of how we developed the main hypotheses that currently guide our research. The aims of our studies are to (1) determine how chronic stress impairs the dendritic morphology of the main nuclei of the rat auditory system, the inferior colliculus (auditory mesencephalon), the medial geniculate nucleus (auditory thalamus), and the primary auditory cortex; (2) correlate the anatomic alterations with the impairments of auditory fear learning; and (3) investigate how the stress-induced alterations in the rat limbic system may spread to nonlimbic areas, affecting specific sensory system, such as the auditory and olfactory systems, and complex cognitive functions, such as auditory attention. Finally, this article gives a new evolutionary approach to understanding the neurobiology of stress and the stress-related disorders.

Keywords: auditory system; depression; fear learning; stress.

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Stress and the psychiatric-related disorders

Hans Selye, an Austro-Hungarian researcher, introduced the concept of stress, which he defined as a nonspecific biological response of an organism to any pressure or demand from the environment (Selye, 1936, 1956). Stress, or general adaptation syndrome, is oriented to restore the homeostasis and to adapt to environment pressure (stressor) (Calabrese et al., 2007; McEwen, 2007). Stress can be positive (eustress) when the stressors are mild, brief, and controllable (Tafet and Bernardini, 2003). Strong, persistent, and uncontrollable stressor may lead to a maladaptive response (distress). Currently, the concept of stress has evolved into the concept of "allostasis", defined as the adaptive process of preserving stability in response to stressful conditions (McEwen and Chattarji, 2004). When the energy cost of adaptation (allostatic load) is too high, stress induces negative consequences (Tafet and Bernardini, 2003; McEwen and Chattarji, 2004).

The organization of stress responses is mainly modulated by the adrenal steroids hormones glucocorticoids (GCs) (McEwen, 2006). Stressors activate the hypothalamus-pituitary-adrenal (HPA) axis, leading to the secretion of GCs from the adrenal glands that are bound to glucocorticoid receptors (GRs) in the peripheral tissues and in the brain (Herman, et al., 1996, 2003; Smith and Vale, 2006).

There is abundant evidence indicating that chronic stress and GC administration affects the brain areas that process the emotional interpretation of sensory stimuli, for example, the limbic system and the prefrontal cortex (Magariños et al., 1998; McEwen and Chattarji, 2004). In animal models, chronic stress and GC induces dendritic atrophy in CA3 pyramidal neurons and decreases neurogenesis at the dentate gyrus of the rat hippocampus, leading to impairments in memory and learning (McEwen et al., 1992; Watanabe et al., 1992; Magariños and McEwen, 1995; McEwen and Chattarji, 2004). In addition, chronic stress decreases spine density and induces apical dendritic atrophy in the pyramidal neurons of layer II/III of the rat medial prefrontal cortex (mPFC) (Cook and Wellman, 2004; Radley et al., 2004). In contrast, chronic stress and GC administration induces hypertrophy of the stellar neurons at the lateral amygdala, affecting the emotional processing of sensory information (Cordero et al., 1998; Vyas et al., 2002, 2003; Mitra and Sapolsky, 2008).

In agreement with animal studies, chronic stress in humans is related to the hippocampal volume atrophy (Pruessner et al., 2005) and alterations in the prefrontal cortex functions (Liston et al., 2009). Clinical studies have shown that chronic exposure to stressful life events is associated with the development of depressive symptoms. These studies strongly support the link between psychosocial stress and major depression (Tafet and Bernardini,

2003; Tafet and Smolovich, 2004; van Praag, 2005). Furthermore, psychosocial stress is a key risk factor for several chronic diseases with high social and economic impact, such as cardiovascular diseases (Niedhammer et al., 1998; Lundberg, 2005; Innes et al., 2007), cancer (Lundberg, 2005; Kemeny and Schedlowski, 2007), diabetes type II (Lundberg, 2005), and addictive behaviors (Bossert et al., 2005).

People exposed to modern life show high levels of psychosocial stress (Maddock and Pariante, 2001). Likewise, adverse conditions at work and in personal life are the main risk factors to developing major depression (Dohrenwend et al., 1992; Cronkite et al., 1998). Human neuroimaging studies have shown that depression in patients is also associated with hippocampal volume atrophy (Sheline et al., 1996; Colla et al., 2007) and the reduction in the volume of gray and white matter of the prefrontal cortex (Rajkowska et al., 1999; Manji et al., 2003). Reductions in the neuronal size and/or a decreased density of glial cells in the orbitofrontal, dorsolateral, and subgenual prefrontal cortex were found in autoptic brains of patients with major depression (Rajkowska et al., 1999; Manji et al., 2003). Structural magnetic resonance imaging performed with depressed patients has shown volume atrophy, functional changes in cerebral blood flow and glucose metabolism in the amygdala (Sheline et al., 1996; Shin et al., 2006; Fales et al., 2008), and the hyperactivation of the amygdaloid complex (Zhong et al., 2011). Another stress-related disorder is associated with hippocampal atrophy (Wang et al., 2010). This evidence is inconsistent with comparable studies that have not shown correlations with the changes in the hippocampal volume (Schuff et al., 2001, 2008). However, ^{1}H magnetic resonance spectroscopic imaging studies have shown that the neuronal density and the metabolism marker N-acetylaspartate are lower in patients with posttraumatic stress disorder (Schuff et al., 2001, 2008). In addition, posttraumatic stress disorder is related to a decreased regional cerebral blood flow in the prefrontal cortex (Shin et al., 2004) and to an elevated response of the amygdala to neutral stimuli (Brunetti et al., 2010). These alterations may contribute to the cognitive deficits (Sapolsky, 2001).

Stress effects on the auditory system and fear learning

Studies on the stress neurobiology have focused on the limbic system and the mPFC (McEwen and Chattarji, 2004). In contrast, we studied whether previously described stress-induced alterations in the limbic system may spread to the nonlimbic regions, affecting specific sensory systems downstream and upstream. First, we chose the epithalamic pineal gland because this brain area expresses a high density of GR (Warembourg, 1975; Meyer et al., 1998) and may be a target of stress-induced damage by GCs (Sapolsky, 2000). Chronic stress decreases the sympathetic innervation of the pineal gland, whereas melatonin concentration increases significantly in chronically stressed rats (Dagnino-Subiabre et al., 2006a,b).

Sensory information from the environment is received in several brain nuclei and undergoes a number of types of processing. The neuronal networks at the mesencephalic, thalamic, and cortical levels carry out different types of sensory information to the amygdaloid complex to acquire emotional processing. Thus, some brain nuclei are specialized to process specific types of somatosensory information; for example, the inferior colliculus (IC) located at the mesencephalon is a major brain nucleus specialized in analyzing auditory information (Figure 1). The brain connections define functions; for example, each sensorial brain nucleus has different levels of connectivity with the amygdala, allowing a different type of emotional processing for each nucleus. Studying the evolution of these connectivities provides interesting data to understand the emotional processing of sensorial information in the brain of stressed animals. For example, auditory efferents from the rat thalamic medial geniculate nucleus (MG, auditory thalamus) are sent directly to the amygdala (McDonald, 1998; Wilensky et al., 2006) (Figure 1). In contrast to the MG, the lateral amygdala receives only indirect projections from the lateral geniculate nucleus (LG) of the visual thalamus (Leroux et al., 1984; McDonald, 1998) (Figure 1). During classic visual fear conditioning, the expression of conditioned fear is produced directly from both the superior colliculus (SC) by the lateral posterior nucleus-lateral amygdala pathway and the retina (Doron and Ledoux, 1999; Shi and Davis, 2001). It is probably the case that such projections are not as robust as the auditory projections from the MG to the lateral amygdala (LeDoux et al., 1990b). Comparable connectivity is found at cortical levels between rat auditory and visual cortices. From the primary auditory cortex (A1), projections are sent directly to the lateral amygdala, whereas the primary visual cortex does not send direct projections to the amygdala (McDonald, 1998) (Figure 1). The visual information, which is analyzed in the visual association cortices, only arrives to the amygdaloid complex through the temporal cortex (McDonald, 1998). On the other hand, outputs are sent directly to the lateral amygdala from the auditory association cortices (McDonald, 1998). This evidence suggests

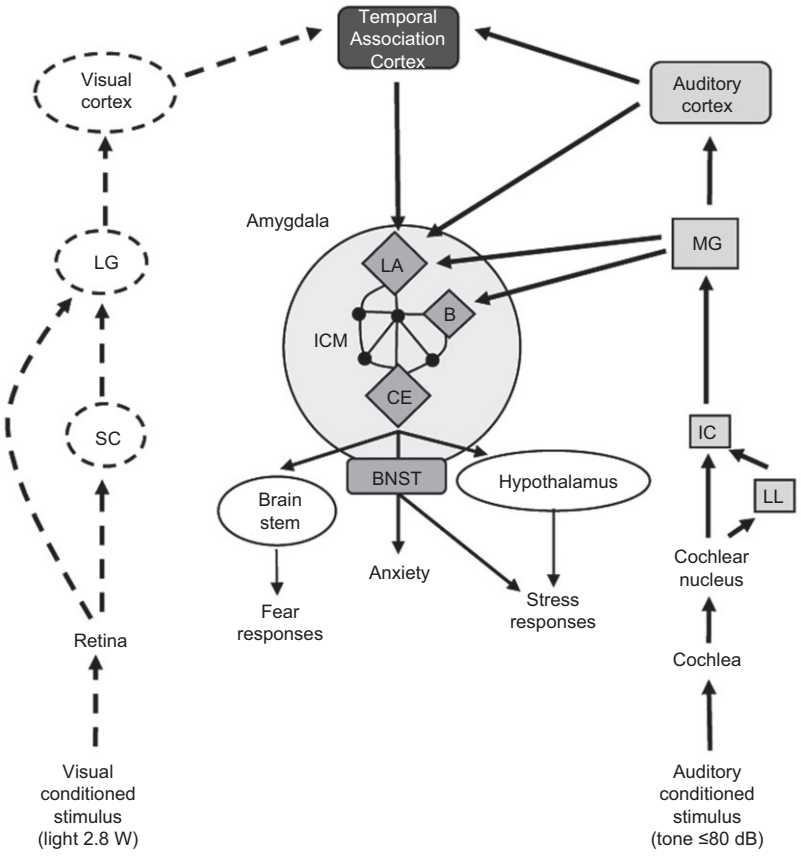

Figure 1 Main ascending neuronal pathway involved in auditory and visual emotional processing in rats.
The auditory and visual systems have direct and indirect connections to the amygdala. This scheme illustrates only the direct connections between the major nuclei of the auditory and visual pathway to the amygdala. Auditory conditioned stimuli (tone, CS; continuous line) are received in the cochlear nucleus and send projections to the LL and IC. From the IC, efferents are sent to the MG and the auditory cortex, where in turn the MG projects glutamatergic inputs to the lateral and basal amygdaloid nuclei. The direct pathway from the MG to the lateral (LA) and basal (B) amygdala is also directly activated by tone >80 dB. Visual conditioned stimuli (light, dotted line) are received in the retina and are then sent to the LG and the SC. From the LG, projections are sent to the primary visual cortex. Information received in the LA and B amygdala is sent to the CE through the intercalated cell masses (ICM). The CE projects to hypothalamic sites and several brain stem nuclei that participate in the stress and fear responses (such as freezing). From the CE, projections are directed to the bed nucleus of stria terminalis (BNST), inducing anxiety.

that the auditory system in rats could be more robustly connected with the amygdala than the visual system.

Rats are nocturnal animals, so their visual sense is of little importance to detect the predators. The rat auditory system is more developed than that of visual animals such as primates, which detect their predators by visual cues as well as by sound. The escape response is a stress response triggered by the hypothalamic activation. A higher connectivity between the subcortical nuclei and the amygdala may induce a faster escape response when rats perceive their predators by auditory cues. This higher connectivity between the amygdala and the auditory system rather than the visual system may have been an evolutionary adaptation to their environment. This major connectivity between the auditory system and the amygdala is also found in visual animals such as primates, which could be a feature of all mammalian groups conserved through evolution, independent of lifestyle (McDonald, 1998).

The findings of neuroanatomic studies on the connectivity between the amygdala and the sensory systems raise the question of whether the auditory system of primates has retained a greater connectivity with the amygdala compared to rats. One possible answer is that vocal communication is more common in the arboreal species of nonhuman primates than the terrestrial species of the primates, because they have less visual contact. An important feature of the anthropoid primates is a larger neocortex than that of other mammals, including the suborder prosimii (e.g., prosimians, lemurs, lorises, galagos, and tarsiers) (Passingham, 1981; Allman and Hasenstaub,

1999). This is apparently associated with the specialized perceptual, cognitive, and social adaptations that characterize this mammalian group (Dunbar, 1992; Kaas, 1995; Barton, 1996; Tomasello and Call, 1997). The lifestyle of these animals could result in an auditory system more connected with the amygdala to activate quickly in response to acoustic danger signals associated with predators. Conversely, gestural communication is a more common type of communication in terrestrial primates, such as chimpanzees, due to their proximity. It has been reported that chimpanzees use distinct gestures in a variety of contexts, for example, during play, grooming, and sexual behavior (Goodall, 1986). Plooij (1978, 1979) analyzed the gestural communication of some primate species. It has been documented that some gestural behaviors could be specific to certain populations, such as the gesture leaf-clipping and the grooming hand-clasp (McGrew and Tutin, 1978; Nishida, 1980; Sugiyama, 1981; Ghiglieri, 1984; Boesch, 1995), with evidence that they are socially transmitted (McGrew and Tutin, 1978; Nishida, 1987). Comparable results have been obtained in other primate species, such as gorillas and siamangs (Pika et al., 2003; Liebal et al., 2004).

Moreover, there is strong evidence that the main type of primate communication is via the auditory system (Gerhardt, 1992). Several acoustic properties of communication signals encode the different kinds of major biological information (Gerhardt, 1992). Indeed, acoustic inputs not only encode different signal categories among primates but also encode information about motivational state (Hauser, 1991; Gouzoules and Gouzoules, 2000); sexual, individual, and group identity (Rendall et al., 1996, 1998; Miller et al., 2001; Weiss et al., 2001); body size; and reproductive status (Fitch, 1997; Semple and McComb, 2000). Interestingly, individual and kin recognition has been demonstrated in some primate species, such as rhesus monkeys (Hauser, 1991; Rendall et al., 1996) and cotton-top tamarins (Miller et al., 2001; Weiss et al., 2001). In addition, it has been suggested that terrestrial primates are able to distinguish between the multiple levels of acoustic information encoded within a single vocal signal (Weiss et al., 2001). On the other hand, changes in the acoustic structure of vocal signals are found in primate species, such as pigtail macaques (Gouzoules and Gouzoules, 1990), vervets (Seyfarth and Cheney, 1986; Hauser, 1989), pygmy marmosets (Elowson et al., 1992), and squirrel monkeys (Lieblich et al., 1980). As well, matrilineal signature in coo vocalizations is found in some primate species, which provides insights into acoustic variations among social primate groups (Gouzoules and Gouzoules, 1990; Hauser, 1991, 1992). In support of this idea, some reports have shown the neural substrate in the primate brain that discriminates the vocal signal type (Ghazanfar and Hauser, 2001), and in populations of captive chimpanzees, group differences in vocalizations have been attributed to social learning (Marshall et al., 1999).

Overall, terrestrial primates have both communication types, gestural and vocal. However, an auditory system more connected with the amygdala than the visual system was possibly required to develop a higher complexity of social interactions (e.g., dominance hierarchies, nonkin alliances, reconciliation, and redirected aggression), extensive kin-biased behaviors (e.g., preferential grooming, affiliation, and cooperation), and social manipulation (Byrne and Whiten, 1988; De Waal, 2000).

If a higher connectivity between the amygdala and the MG has been selected throughout evolution, then neuronal plasticity at the lateral amygdala could affect the dendritic morphology of the auditory thalamus. An example of this situation takes place in Pavlovian conditioning. There is strong evidence that the lateral amygdala has a key role in the acquisition and consolidation of emotional memories by the Pavlovian auditory fear conditioning (LeDoux et al., 1990b; Campeau and Davis, 1995; Amorapanth et al., 2000). The acquisition of emotional memories in the amygdala is associated with neuronal plasticity in both the lateral amygdala and the MG (Maren et al., 2001; Poremba and Gabriel, 2001) (Figure 1). These brain areas exhibit an associative plasticity of spike firing during auditory fear conditioning (Maren et al., 2001). I hypothesize that the auditory system is affected in some neuropsychiatric disorders related to increases in the amygdala activity. In rats, chronic stress produces dendritic hypertrophy of the excitatory pyramidal and stellate neurons of the amygdaloid basolateral complex (BLA) (Vyas et al., 2002) and does not affect the neuronal morphology of the central amygdaloid nucleus (CE) (Vyas et al., 2003) (Figure 1). I used this evidence to propose the hypothesis that auditory fear learning is impaired in chronically stressed rats (Dagnino-Subiabre et al., 2005). Our first experiment analyzed the auditory and visual learning in control and stressed rats. We found that chronic stress affects both auditory and visual avoidance conditioning, but the stressed rats showed a stronger impairment in auditory conditioning than in visual conditioning (Dagnino-Subiabre et al., 2005).

It is likely that chronic stress-induced dendritic change in the hippocampus and amygdala could be related to impairments in both auditory and visual fear conditioning. However, the stronger effect on auditory conditioning compared with the visual conditioning may be explained by an additional damage in the auditory neuronal pathway

in the brain of stressed rats. We studied in Golgi preparations the effect of stress on the neuronal morphology of the IC, a mesencephalic area key in the regulation of acoustic processing (Pollak et al., 2003), and the superior colliculus (SC), an important relay in the visual pathway (Figure 1). We found that stress-induced dendritic atrophy in the IC did not affect the dendritic morphology of SC neurons (Dagnino-Subiabre et al., 2005) (Figure 1). Fifteen days after stress, the IC neurons restored their structure completely, showing a high level of neural plasticity that correlated with an improvement in acoustic and visual learning during an avoidance conditioning test (Dagnino-Subiabre et al., 2005). In addition, we found that chronic corticosterone treatment induces dendritic atrophy of flat neurons in the IC and impairs the auditory fear learning in rats (Dagnino-Subiabre et al., 2012). IC atrophy may decrease the ability of those neurons to receive and deliver the auditory information to the auditory cortex and limbic areas via the thalamus (Figure 1).

The emotional processing of the acoustic information depends on the intensity of the acoustic stimulus (McDonald, 1998; Wilensky et al., 2006). Acoustic stimuli equal to or higher than 80 dB are processed at the subcortical level through the neuronal pathway formed by the cochlea nucleus and superior olivary complex-lateral lemniscus (LL) (Figure 1). The IC receives all projections from these nuclei, which are then sent to the MG. Part of the auditory information received in the MG is sent directly to the lateral amygdala (McDonald, 1998; Wilensky et al., 2006) (Figure 1). The posterior intralaminar nucleus is another thalamic nucleus that receives inputs from the IC and the efferents are sent directly to the amygdala (LeDoux et al., 1990a; Turner and Herkenham, 1991). Auditory stimuli equal to or lesser than 80 dB must be associated with an aversive unconditioned stimulus (US), such as foot shock, to acquire the ability to elicit conditioned fear responses (Monfils et al., 2009). On the other hand, acoustic stimuli equal to or higher 90 dB are sent from the dorsal nucleus of the LL to the posterior thalamic nucleus (PO), located just medially to the posterior intralaminar nucleus (Kudo et al., 1983; Paré et al., 2004). The PO also receives auditory projections from the nucleus of the brachium of the IC (Kudo et al., 1983). The PO efferents are sent directly to the CE and to the primary somatic sensory cortex, indicating the possibility that the CE receives auditory input from the thalamus (Paré et al., 2004). Through this neuronal pathway, the CE is activated and fear responses, such as freezing, are performed independently of the pathway formed by the IC-MG-auditory cortex. In this context, we analyzed the chronic stress effects on the processing of conditioned stimulus (CS; ≤80 dB) and US (≥90 dB) by morphologic, fear conditioning and the acoustic startle response (ASR) studies. Fifteen days of restraint stress-induced dendritic atrophy in the magnocellular neurons of the MG did not affect fear conditioning when 80 dB tones were used as CS (Dagnino-Subiabre et al., 2009) (Figure 1). A prolonged or more intense stress, such as restraint stress for 21 days (6 h a day), increased freezing compared with control rats through fear conditioning trials (Conrad et al., 1999). Conversely, freezing was significantly enhanced by restraint stress during the visual conditioning compared with control animals (Dagnino-Subiabre et al., 2009). However, this alteration was not associated with the ability to elicit a conditioned fear response (Dagnino-Subiabre et al., 2009). Restraint stress did not affect unconditioned responses such as ASR, prepulse inhibition (PPI), and escape behavior. As well, restraint stress did not affect the morphology of the PO (Dagnino-Subiabre et al., 2009). Two types of stress protocols that were more intensive than restraint stress, chronic variable stress and psychosocial stress, produced an increase in ASR and PPI in rats (Maslova et al., 2002; Zoladz et al., 2008).

At the cortical level, restraint stress produced basilar dendritic atrophy in the pyramidal neurons of layer II/III and in the apical dendrites of the pyramidal neurons of layer V/VI in the A1 (Bose et al., 2010). Restraint stress did not affect the morphology of the visual thalamus and cortex and the PO (Dagnino-Subiabre et al., 2009; Bose et al., 2010). These results suggest that auditory conditioned stimuli may be processed in part independently of the IC and MG in the stressed rats and sent to the amygdala via the PO, establishing an association with the somatosensory US inducing unconditioned fear. These alterations could affect the emotional processing of the auditory stimuli and alter the environmental adaptation (Dagnino-Subiabre et al., 2009).

Chronic stress induces dendritic atrophy in the rat auditory cortex and this brain area is key for some complex cognitive behaviors, such as auditory attention and decision-making (Jaramillo and Zador, 2011). Given this evidence, we hypothesize that chronic stress in rats impairs complex cognitive functions such as auditory attention. Alterations in complex cognitive functions, for example, attention and decision-making, are found in persons suffering psychosocial stress and stress-related disorders, such as posttraumatic stress disorder and major depression (Gotlib and McCann, 1984; Mialet et al., 1996; Ottowitz et al., 2002; Kähkönen et al., 2007; Simoens et al., 2007; Kimble et al., 2010). Furthermore, using electroencephalographic recording demonstrates that psychosocial stress in humans decreases general sound processing (Simoens

et al., 2007). As well, studies closely related to our basic research suggest that depression in patients is accompanied by impaired auditory processing, which seems to improve with reduction in depressive symptoms (Michael et al., 2004; Tollkotter et al., 2006; Christ et al., 2008). The main function of the human auditory system is speech and language processing (Horwitz and Braun, 2004). It is possible that these functions are particularly affected in stress-related disorders. Depressive patients frequently present language deficits such as anomia (or difficulty finding words) and naming errors (substitution by semantically related words) (Emery and Breslau, 1989; Georgieff et al., 1998). In this line, electrophysiologic studies have shown disturbances in auditory event-related potentials, such as higher P300 latency, in patients suffering from major depression (Vandoolaeghe et al., 1998).

Cross-talk between stress and the immune system

Living organisms try to adapt to internal or external stressors that disturb homeostasis (Cannon, 1929). The sympatho-adrenal system and the HPA axis coordinate the physiologic basis of homeostasis and adaptation. On the other hand, chronic stress often impairs adaptation, which in turn induces the pathologic changes in the endocrine and immune systems, characterized by the hypertrophy of the adrenal and pituitary glands, and the abnormal changes in the composition of immune cells (Arborehuis et al., 1999). The metabolic changes in chronically stressed animals are initiated by the hypersecretion of the GCs and the hyperactivity of the sympatho-adrenal system. These changes also involve the activation of peripheral and central macrophages that increase proinflammatory mediators (Brambilla, 2000). Lymphocytes and monocytes contain adrenoceptors that respond to the catecholamines released from the adrenal medulla during stress (Brambilla, 2000). GCs also reduce lymphocyte function by stimulating GRs located on the outer membrane (Croiset et al., 1987; Leonard and Myint, 2009). Moreover, the thymus gland and the bone marrow are directly innervated by noradrenergic afferents that affect the development of immune cells and decrease the release of anti-inflammatory cytokines such as interleukin (IL)-4 and IL-10 (Leonard and Song, 1999).

There is abundant evidence that the immune system directly or indirectly can modulate both central neurotransmitters and endocrine function (Leonard and Song, 1999). For example, proinflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor-α are released from monocytes, macrophages, and other immune cells in the periphery and from microglia and astrocytes in the brain. These molecules strongly affect the central monoamine functions and activate the HPA axis (Song et al., 1994). For instance, proinflammatory cytokines activate specific cytokine receptors on neurons and glial cells and thereby directly influence brain function (Maes et al., 1992; Leonard and Song, 1999). In support of this idea, the systemic administration of IL-1 in rodents increases the plasma adrenocorticotrophic and corticosterone. IL-6 and tumor necrosis factor-α also activate the HPA axis, but their effects are less potent compared with IL-1.

It is possible that proinflammatory cytokines released under chronic stress can indirectly affect the auditory system functions. Chronic stress increases the release of proinflammatory cytokines from astrocytes, which in turn increases both the HPA axis activity and the plasma corticosterone levels. The BLA shows high concentrations of GRs (Gray and Bingaman, 1996); therefore, proinflammatory cytokines-induced increases of plasma corticosterone levels could affect the neuronal activity in BLA by the GRs. In this way, proinflammatory cytokines can maximize the dendritic hypertrophy induced by the chronic stress in BLA (Vyas et al., 2002). Corticosterone binds to cytosolic GRs in the BLA, inducing GR dimerization and translocation to the nucleus, thereby increasing the gene expression of proplasticity genes, such as neuronal cell adhesion molecules, NCAM and L1 (De Kloet et al., 1998; Sandi, 2004). Moreover, the complex formed by corticosterone and GRs increases the nuclear translocation of nuclear factor-κB, which could increase the expression of neurotrophins, such as brain-derived neurotrophic factor and neurotrophin-3, in the neurons of the basolateral nucleus of amygdala (Reichardt, 2006). These molecules are implicated in neurite extension, cell survival, and synaptic plasticity (Kiss et al., 2001). In support of this idea, corticosterone treatment induces the dendritic hypertrophy in BLA (Mitra and Sapolsky, 2008). The auditory thalamus and BLA exhibit associative plasticity (Maren et al., 2001), and perhaps in this way, the neuronal changes in BLA induced by proinflammatory cytokines could affect the auditory system functions.

Chronic stress and the olfactory system

Another sensory system that shows strong neuronal connectivity with the amygdaloid complex is the olfactory

system (Scalia and Winans, 1975; Shipley and Ennis, 1996). Indeed, the rat olfactory amygdala, located in the superficial nuclei of the amygdaloid complex, includes several subnuclei that receive afferents from the olfactory tract (Paxinos, 2004). Interestingly, in animal models of chronic stress, such as chronic unpredictable mild stress, the stressed animals show olfactory bulb atrophy, reduced neurogenesis, and presynaptic dysfunction in the olfactory bulb (Hitoshi et al., 2007; Yang et al., 2011). This evidence is in agreement with clinical data showing that depression in patients is associated with decreased olfactory sensitivity and olfactory bulb volume atrophy, which seems to improve after successful treatment (Pause et al., 2001; Pollatos et al., 2007; Atanasova et al., 2008; Negoias et al., 2010).

Conclusions

The two sensory systems more connected with the amygdaloid complex are the auditory and the olfactory. In addition to stress-induced alterations in the limbic system and the mPFC, the auditory and olfactory systems are also sensitive impairment by chronic stress. This evidence suggests that the chronic stress effects in the rat brain are broader than previously thought and affect specific sensory systems. The morphologic alterations induced by chronic stress in the rat auditory system impair auditory fear learning. Currently, we are evaluating the hypothesis that chronically stressed animals show impairments in the complex cognitive functions such as auditory attention, which may alter the environmental adaptation. Comparable behavioral and morphologic alterations could be induced by psychosocial stress in humans and have a role in the development of major depression. Our study opens a new approach to understanding the neurobiology of stress and the stress-related disorders.

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