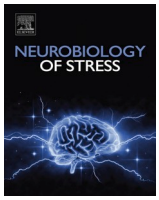
Neurobiology of Stress 19 (2022) 100460

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: www.elsevier.com/locate/ynstr



Impact of stress on inhibitory neuronal circuits, our tribute to Bruce McEwen

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A B S T R A C T

This manuscript is dedicated to the memory of Bruce S. McEwen, to commemorate the impact he had on how we understand stress and neuronal plasticity, and the profound influence he exerted on our scientific careers. The focus of this review is the impact of stressors on inhibitory circuits, particularly those of the limbic system, but we also consider other regions affected by these adverse experiences. We revise the effects of acute and chronic stress during different stages of development and lifespan, taking into account the influence of the sex of the animals. We review first the influence of stress on the physiology of inhibitory neurons and on the expression of molecules related directly to GABAergic neurotransmission, and then focus on specific interneuron subpopulations, particularly on parvalbumin and somatostatin expressing cells. Then we analyze the effects of stress on molecules and structures related to the plasticity of inhibitory neurons: the polysialylated form of the neural cell adhesion molecule and perineuronal nets. Finally, we review the potential of antidepressants or environmental manipulations to revert the effects of stress on inhibitory circuits.

1. Remembering Bruce: a serendipitous voyage

1.1. Serendipity

Bruce and I (Juan Nacher) talked sometimes about this word, and its influence on the shaping of science and life. Different serendipitous events led me to join Bruce's lab and I only can be grateful for them to have happened. It is a privilege for me to have collaborated with him, to have shared many conversations and to have enjoyed his knowledge and his wisdom. He always gave me freedom to explore and supported me in every step of my career. His vision of the brain as a plastic structure and of the impact of adverse experiences on this plasticity, changed my research perspective. Serendipity also allowed me to meet a group of dear friends and scientists who were at the time in Bruce's lab. I cannot mention them here because the list is long and it is not the place, but, as Bruce, they will always be in my heart.

Although I joined Bruce's lab in 1998 to study adult hippocampal neurogenesis and its regulation by NMDA receptors (NMDAR), serendipity changed the direction of my career and that of the researchers that have worked in my laboratory (many of them, "second order mcewenites", are involved in this review). While in Bruce's lab we started to work with 2 molecules, in which we have focused our research the last 20 years, doublecortin and the polysialylated form of the neural cell adhesion molecule (PSA-NCAM). In the late 90's we were looking for markers of immature neurons to monitor the incorporation of new neurons to the adult dentate gyrus (DG) and to observe the influence of different intrinsic and extrinsic factors on this adult neurogenesis, following the work that Liz Gould and Heather Cameron had started in Bruce's lab (Cameron et al., 1993; Cameron and Gould, 1994; Gould et al., 1992)). The story behind the selection of PSA-NCAM is also touched by serendipity. I mentioned the molecule to Bruce and he told me that he was a very good friend of Urs Rutishauser, one of the leading researchers on PSA-NCAM (Rutishauser, 2008), and played tennis with him every week. From there we started a collaboration and friendship

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https://doi.org/10.1016/j.ynstr.2022.100460
Received 15 February 2022; Received in revised form 22 April 2022; Accepted 10 May 2022
Available online 13 May 2022

that has produced relevant results and, more important for me, wonderful hikes in the Alps and a rediscovery of Gaudi in Barcelona …

Through the influence of my friends and colleagues Francisco José Martínez-Guijarro and José Miguel Blasco-Ibañez and their passion for GABAergic interneurons, we soon realized that many of the cells that expressed PSA-NCAM in the adult brain were in fact mature inhibitory neurons, not only in rodents (Gómez-Climent et al., 2011; Nacher et al., 2013; Varea et al., 2005), but also in the human brain (Emilio Varea et al., 2007b). Here my friend and colleague Emilio Varea played a crucial role. From there, different studies have allowed us to observe the influence of PSA-NCAM on the structure, connectivity and physiology of interneurons (Castillo-Gómez et al., 2011; Gómez-Climent et al., 2011; Guirado et al., 2014a; Nacher et al., 2013) and its involvement in psychiatric disorders (Gilabert-Juan et al., 2012b; Varea et al., 2012). Still working in collaboration with Bruce we found that stress had a strong impact on PSA-NCAM expression (J; Gilabert-Juan et al., 2011. Nacher et al., 2004a; Pham et al., 2003). Carmen Sandi was also at the time involved in this line of research (Cordero et al., 2005; Sandi et al., 2001). I met Carmen, in part also by serendipity, and we started a collaboration and friendship that has lasted for many years and was shared with Bruce. I know Carmen is missing him as much as I do.

The impact of PSA-NCAM on the structure and connectivity of interneurons and the effects of stress led us to start exploring whether this adverse experience could also change the structure and connectivity of

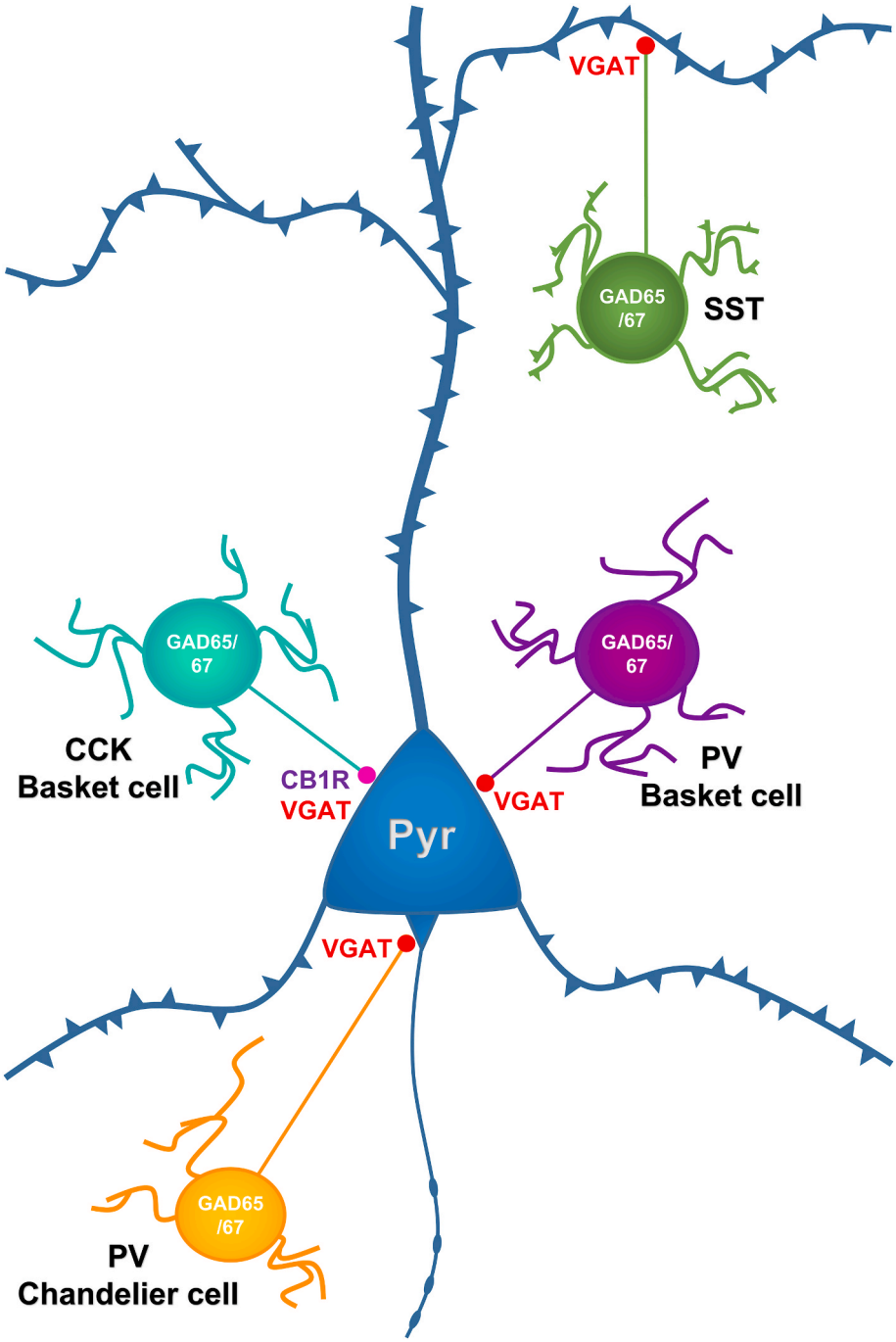

Fig. 1. Overview of the main interneuron subpopulations considered in this review (CCK+, SST+, basket PV+ and chandelier PV + cells), along with their subcellular targets. The expressed molecules that are discussed in this manuscript are also shown (GAD65/67 and VGAT are expressed by every GABAergic neuron, while CB1R is expressed presynaptically in CCK + interneurons of the neocortex).

interneurons, both during adulthood and during early life. Bruce was very supportive when we started this line and offered valuable input on many of the manuscripts. The present review recapitulates our findings and those of many other labs involved in studying the impact of stress on inhibitory neuronal circuits. I kept contact with Bruce and we talked by phone or videoconference at least once a year. In fact, we were starting to work on a review on the impact of stress on inhibitory neurons. Unfortunately, many other projects crossed this road and we could not finish it. I hope that this review can serve as a modest tribute to Bruce and to what he meant for us.

2. The diverse world of inhibitory neurons

In a given cerebral region excitatory or principal neurons are very uniform in terms of structure, connectivity, neurochemistry or physiology. By contrast, inhibitory neurons appear in very diverse flavors. From here on, for practical purposes, we will use the term interneuron to refer to inhibitory or GABAergic neurons, since they mainly express this neurotransmitter. They can be identified by its expression and also by that of the enzymes leading to its synthesis from glutamate, the glutamic acid decarboxylases 65 and 67 (GAD65 and GAD67). Inhibitory synapses can be identified by specific inhibitory presynaptic markers, such as the vesicular GABA transporter (VGAT). There are several recent excellent reviews on interneuronal diversity and the reader can find detailed descriptions of their development, molecular profile, connectivity and physiology (Freund and Buzsáki, 1996; Hájos, 2021; Lim et al., 2018; Tremblay et al., 2016). The subpopulations are defined by their differential expression of calcium binding proteins, neuropeptides, neurotransmitter receptors and the target of their axons, which define their structure, connectivity and physiology. A schematic diagram of the principal interneuronal subpopulations of the cerebral cortex and their connectivity can be found in Fig. 1. Most reports on the effects of stress on interneurons have been focused on interneurons expressing the calcium binding protein parvalbumin (PV) or the neuropeptide somatostatin (SST). PV + neurons are fast spiking neurons that can be divided in 2 different subpopulations: i) basket cells, which innervate the perisomatic region of excitatory neurons and ii) chandelier cells, which innervate the axon initial segment of excitatory neurons. Very few studies on the effects of stress have distinguished between those 2 subpopulations. Some studies have also studied another population of PV-basket interneurons, those expressing the neuropeptide cholecystokinin (CCK). These cells are very interesting because, at least in the cerebral cortex, they express cannabinoid type 1 receptors (CB1R) in their synaptic boutons. SST + interneurons target the distal dendritic segments of excitatory neurons. There are other types of interneurons characterized by the expression of different calcium binding proteins and neuropeptides, but since the studies on the impact of stress on these cells are scarcer, we will mention them specifically in each of the studies.

In 1968, Bruce demonstrated that corticosterone also binds to glucocorticoid receptors in extrahypothalamic regions (McEwen et al., 1968). Many reports afterwards have described the presence of these receptors in principal or glutamatergic neurons in several areas of the brain. However, the literature on the expression of these receptors in interneurons is very scarce and comprehensive studies are still lacking. First reports indicated that type II glucocorticoid receptors appear to be absent from the hippocampal interneurons of male rats, but that some diffuse cytoplasmic labeling could be observed in the stratum oriens of CA3 and CA1 (Ahima et al., 1992). Peptidergic interneurons in the neocortex and the hippocampus lack glucocorticoid receptors, although these receptors are present in some amygdaloid nuclei (Cintra et al., 1991), particularly in the central amygdala (CeA) (Honkaniemi et al., 1992). Posterior reports failed to find glucocorticoid receptors in calretinin (CR) expressing interneurons in the hippocampus (Patel and Bulloch, 2003) or described lower expression in interneurons than in projection neurons in the nucleus interpositus (Wilber and Wellman, 2009). By contrast with these previous studies, a recent report has described that more than 60% of GAD67+ and CR + inhibitory neurons and half of PV + neurons in the infralimbic cortex, a region of the medial prefrontal cortex (mPFC), express glucocorticoid receptors. However, these receptors were lacking in interneurons expressing calbindin (CB), SST and CCK (McKlveen et al., 2016).

3. Impact of stress on inhibitory neurons

Different factors influence the effects of stress, including its intensity, duration, controllability, the life stage in which it is experienced, the sex of the individuals suffering it, among others. For this reason we have tried to analyze separately the impact of stress on inhibitory circuits taking into account these factors. We will first focus on the effects of short term or acute stress and then we will review evidence of the effects of chronic stress. In the chronic stress chapter, we will analyze separately that occurring during early life and that during adulthood. For organizative reasons, we will analyze separately the effects of stress in different regions of the brain, particularly in the limbic system. We then will review the effects of stress on PSA-NCAM and perineuronal nets (PNNs), other structures involved in interneuronal plasticity. Finally, we will briefly discuss data on the potential of antidepressants and enriched environments to reverse the effects of stress on interneurons. It is important to note that our review is particularly focused upon the effects of stress on the presynaptic aspect of the inhibitory circuit. However, the postsynaptic element of this circuit, including GABA receptors or the regulation of the Cl-gradient, also play a relevant role in the stress response and deserves further analysis (Barberis, 2020; Maguire, 2014; Skilbeck et al., 2010).

3.1. Acute stress

The effects of acute stress on the physiology and structure of interneurons have been explored in different models, from the application of corticosterone (Duvarci and Paré, 2007), to the restraint during a single period, ranging from 30 min to 24 h (Hu et al., 2010; Pesarico et al., 2022), or other challenging situations such as forced swimming for 5 min (Yu et al., 2018). Nonetheless, it is important to note that these studies are very scarce and most acute stress models have explored exclusively effects on excitatory neurons (Kim et al., 2014; Mitra et al., 2005; Shinohara et al., 2018).

In rat hippocampal slices, the rapid activation of glucocorticoid receptors by dexamethasone facilitates GABAergic transmission, increasing the frequency but not amplitude of spontaneous inhibitory postsynaptic currents (sIPSCs) in the CA1 region through nitric oxide (NO) retrograde release from pyramidal neurons (Hu et al., 2010). This effect was also replicated after 30 min of restraint stress (Hu et al., 2010). Other acute stress models in adult male mice (5 min of forced swimming and 30 min of restraint) showed an increased activity of dorsal CA1 interneurons and an impairment of spatial memory. Moreover, the chemoactivation of these CA1 interneurons recapitulated this memory impairment (Yu et al., 2018). Another study using male rats found an increase in GAD67 mRNA expression in CA1 and DG, as well as in GAD65 mRNA in the DG after 60 min of restraint (Bowers et al., 1998). Regarding the effects on specific interneuronal populations, 2 h of restraint or cold exposure (4 °C) did not affect the density of PV + cells in the hippocampus of adult male rats (Filipović et al., 2018). By contrast, the exposure to 30 min of restraint produced an increase in the expression of SST mRNA and the number of SST + cells in the DG of male rats (Arancibia et al., 2001). Moreover, in the DG of adult male rats exposed to 1 h of restraint, the number of cells expressing NPY mRNA was increased 6 h after stress, but returned to control levels 24 h later (Conrad and McEwen, 2000). Conversely, the intranasal administration of NPY reversed depressive-like behavior after a single stress period in adult rats (Serova et al., 2014).

Regarding the effects of acute stress on the amygdala, application of corticosterone on rat brain slices during 20 min revealed an

enhancement in the excitability of pyramidal basolateral amygdala (BLA) neurons and a decrease in the $GABA_A$ inhibitory postsynaptic potentials (IPSPs) (Duvarci and Paré, 2007). On the other hand, 2 h of restraint produced an increase in the expression of c-fos in PV+ and CB + cells, remaining unaltered in CR + interneurons of the BLA of male rats (Reznikov et al., 2008). Considering the long term effects of acute stress during adulthood, we have recently reported a decrease in the density of PV + cells in the BLA 35 days after 24 h of restraint (Pesarico et al., 2022). Moreover, we have found interesting effects depending on the interneuronal population and the sex. While there was no effect in the perisomatic inhibition on excitatory neurons of male mice, the PV + cells of female mice displayed a differential response to stress depending on their target: i) we found an increase in the density of PV + perisomatic puncta on Thy1+ pyramidal neurons that project to the infralimbic region of the mPFC, the nucleus accumbens and the bed nucleus of the stria terminalis and mediate fear inhibition (Jasnow et al., 2013), whereas ii) the density of PV + puncta on Thy1-neurons that project to the CeA, and promote fear (Jasnow et al., 2013), were decreased. The other type of basket cells, the CCK + interneurons, were also exclusively altered in female mice, in which the density of their perisomatic puncta on both Thy1+ and Thy-cells was reduced (Pesarico et al., 2022).

The effects of acute stress on interneurons of the PFC are still poorly explored in animal models. After 30 min of restraint in male rats, the endocannabinoid system is activated through the CB1R (present in the synaptic contacts of CCK + cells) and this causes a disinhibition in the mPFC and contributes to termination of stress response (Hill et al., 2011). A recent study has found that acute restraint stress enhances, through $mGlu_5$ receptors, the synaptic strength of the BLA projection onto SST + cells in the PFC, both in male and female mice (Joffe et al., 2022).

Other studies have suggested multiple effects of acute stress on GABAergic interneurons located outside the classical stress-related regions. After 30 min of restraint, a stress-induced oscillation generated by ventral tegmental area GABAergic projections to nucleus accumbens mediated blunt reward-seeking (Lowes et al., 2021). As occurs in the hippocampus, the frequency of sIPSCs on the paraventricular nucleus of the hypothalamus also increased after 30 min of restraint, suggesting an important role of GABAergic transmission in the modulation of the HPA axis (Inoue et al., 2013). Another study has found that 60 min of restraint stress increased GAD67 mRNA expression in some stress-related regions outside the limbic system, such as the arcuate and dorsomedial hypothalamic nuclei, the medial preoptic area and the bed nucleus of the stria terminalis, whereas GAD65 mRNA expression was only increased in the latter region (Bowers et al., 1998).

In summary, a robust finding of most studies is an increased inhibitory activity immediately after the exposure to acute stressors. Due to the wide diversity in the connectivity and firing patterns of interneuronal populations, this generalized activation would affect in multiple ways the excitatory/inhibitory balance throughout several brain regions. This shift, in turn, would contribute to the numerous behavioral alterations reported after acute stress, such as the impairment of spatial memory, increased anxiety and impaired reward-seeking. Nonetheless, the specific impact on the structure and connectivity of interneuronal populations, attending to their diversity, has been barely explored. There is also a considerable lack of studies on the long-term effects of an acute stressful event on interneurons (Pesarico et al., 2022) and this can add valuable information about the role of these inhibitory neurons in the development of psychopathologies, such as post-traumatic stress disorder.

3.2. Chronic stress

3.2.1. Chronic stress during early life

3.2.1.1. Prenatal stress. Stress suffered by mothers during gestation poses a significant risk factor for neuropsychiatric disorders in the offspring, including schizophrenia (Ellman et al., 2019; Levine et al., 2016; Lipner et al., 2019), autism spectrum disorder (Beversdorf et al., 2019; Walder et al., 2014) and major depression (Dagyte et al., 2009). Interestingly, all these neuropsychiatric disorders have been associated with abnormalities in the adult GABAergic system, although the mechanisms by which these changes occur are still not understood (Benes and Berretta, 2001; Möhler, 2012; Rapanelli et al., 2017). In this regard, preclinical studies are indispensable to achieve this goal.

Rodent models of prenatal stress are mainly based on the exposure of the fetus to glucocorticoids, either by the administration of synthetic glucocorticoids to the pregnant female (dexamethasone injections) or by the exposure of the mother to different stressors during the gestational period: restraint or immobilization, continuous light exposure, or chronic unpredictable stress (CUS) (Mañas-Ojeda et al., 2020) for review). Importantly, all these models have been able to replicate some of the behavioral abnormalities observed in the offspring of women subjected to gestational stress. These include anxiety, depressive-like behavior, decreased social preference and learning and memory deficits (Weinstock, 2017) for review).

Repeated acute stress within a plexiglass restraint is still the most popular stressor used in pregnant rodents (Weinstock, 2017). Using this stressor during critical periods of inhibitory neuron development (from E12 to E21), Stevens et al. demonstrated that prenatal stress delays GABAergic neuroblast migration in the mice developing neocortex (Stevens et al., 2013). Although they showed that this aberrant migration did not affect the total number of GABAergic neurons in the adult PFC and hippocampus, the proportion of PV + neurons was altered in juvenile and adult brains. However, all the evaluations were performed on male offspring (Lussier and Stevens, 2016; Uchida et al., 2014).

Gestational restraint stress in rats (from E14 to E21) also promoted excitation/inhibition (E/I) imbalances in the rat adult PFC (in males but not females) and amygdala (in both sexes). In the PFC the balance was shifted towards excitation, while in the amygdala the shift was towards inhibition (Marchisella et al., 2021). A decreased density of PV + neurons and PV + neurons surrounded by PNNs was also observed in the PFC of P21 male mice exposed to prenatal stress (from E15 to E17.5). Remarkably, these alterations were matched by the enhanced and prolonged GABA action that could compensate for the decreased density of PV + neurons (Wang et al., 2018). This might be one of the causes of the E/I imbalance associated with prenatal stress. When restraint stress was applied in an earlier time window (from E7-E21), male rats showed increased levels of DNA methyltransferase (DNMTs) in GABAergic neurons compared to controls, both at birth and in adulthood. Importantly, the overexpression of DNMT in GABAergic neurons was associated with a decrease in GAD67 expression in the PFC and hippocampus of prenatally stressed mice in early and adult life (Matrisciano et al., 2013). The same epigenetic effect was observed in adulthood in the BLA of prenatally stressed female mice (E10-21) and was accompanied by an increase of postsynaptic neuronal excitability in the cortical-basolateral amygdala (Zhu et al., 2018).

In summary, prenatal stress impacts interneuronal development, particularly that of PV + cells, and these effects may have long-lasting consequences on the E/I balance, specially in the cerebral cortex.

3.2.1.2. Stress during infancy and adolescence. Early life experiences are crucial in healthy brain development (Hensch, 2004). Clinical and preclinical studies have demonstrated that exposure to adversity during childhood and adolescence have a lasting impact on brain maturation and functioning, specifically in three key brain regions known to be highly sensitive to stress: the hippocampus, the amygdala, and the PFC. In fact, stress or trauma suffered during these periods, such as abuse, neglect and loss are well-established risk factors to develop a multitude of neuropsychiatric disorders, including schizophrenia, anxiety, and major depression (Danese and McEwen, 2012; Heim and Binder, 2012).

3.2.1.3. Stress during infancy. Because the interaction between parents and their progeny plays a key role in the maturation of neuronal circuitry, the great majority of rodent models of perinatal stress are based on disturbed maternal care (Novais et al., 2017). By far, the most investigated models of disturbed maternal care are the maternal separation protocols, which are well-characterized analogs to childhood neglect in humans (Lehmann and Feldon, 2000; Lupien et al., 2009) and the limited nesting and bedding paradigm, which causes disruption of maternal care (Molet et al., 2014). In both models, age-, sex- and region-specific alterations in interneurons have been described, specially on PV expressing cells and their PNN enwrapping, as we will discuss further in the next chapter (Gildawie et al., 2020; Guadagno et al., 2020; Manzano Nieves et al., 2020). Maternal separation reduced PV expression in the PFC (do Prado et al., 2016) and DG of the hippocampus and increased it in the BLA (Seidel et al., 2008) during adolescence in male rats. Interestingly, these results coincided with alterations in the density of PNNs enwrapping PV + neurons in these regions ((Gildawie et al., 2020); see (Spijker et al., 2020) for review). Limited bedding also increased PV expression in the BLA of male rats, but only during infancy (P21) (Manzano Nieves et al., 2020), and returned to normal levels during adolescence and adulthood (Guadagno et al., 2020; Manzano Nieves et al., 2020; Santiago et al., 2018).

There are still few studies that focus their attention on other subpopulations of interneurons. Maternal separation stress decreased the density of CB+ and CR + interneurons in the paraventricular nucleus of the hypothalamus, but increased it in the hippocampus and lateral amygdala of adolescent male rats (Giachino et al., 2007). When looking for age- and sex-specific changes in the expression of CB and CR proteins after maternal deprivation in rats, Xu et al. reported an increase of both proteins in the hippocampus during infancy (P21-25) but a decrease during adolescence (P30-35) only in males. Females did not show changes in hippocampal CR expression associated with maternal separation. Regarding CB expression in the hippocampus of female rats, maternal separation induced an increase during infancy that reverted to normal during adolescence (Xu et al., 2018). Limited bedding was also associated with increased levels of CR protein in the BLA of infant male rats, which recovered during adolescence and adulthood. In the PFC, limited bedding increased CR and CB expression, but again only during infancy (Manzano Nieves et al., 2020). It is also interesting to mention that maternal deprivation led to increased CB1R expression in this cortical region, which is mainly located in the synapses of CCK + basket interneurons (Marco et al., 2014).

3.2.1.4. Stress during adolescence. Adolescence can be considered a sensitive period for social development, characterized by heightened sensitivity to social stimuli and the increased need for peer interaction (Orben et al., 2020). Normal social and emotional development needs physical interaction with conspecifics; thus, it is not surprising that among the numerous rodent models of adolescent stress, the post-weaning social isolation model is one of the most widely used (Mumtaz et al., 2018). The number of PV expressing interneurons was decreased in the PFC, amygdala and CA1 of isolated animals (Castillo-Gómez et al., 2017; Gildawie et al., 2021; Klimczak et al., 2021; Lukkes et al., 2012). Similarly, female rats isolated for 11 weeks after weaning displayed lower numbers of PV+ and CB + interneurons in the hippocampus, while no alterations could be found on CR expressing interneurons (Harte et al., 2007).

Exposing rats to CUS by using fear-inducing stressors (open field, fox-odor, elevated platform) during adolescence, induced changes in several behavioral domains during adulthood, including pathological aggression, sociability deficits, and increased anxiety and novelty reactivity (de Boer, 2018). This model also led to a significant increase in the density of VGAT immunoreactive puncta in the mPFC, which could be observed when considering both sexes together and in females, suggesting a higher susceptibility of females to peripubertal stress (Bueno-Fernandez et al., 2021). Other studies in male mice, using as stressors a combination of social isolation and forced swimming during adolescence, found a trend towards a reduction in VGAT mRNA, but not of GAD67 or gephyrin in adult individuals (Page et al., 2018). It has been hypothesized that the stress-induced hypoactivity of the PFC may be due to an increased activation of PV expressing cells (Page and Coutellier, 2018). Different experiments using peripubertal stressors in male mice have failed to find differences in the number or density of PV expressing interneurons in the adult mPFC (Bueno-Fernandez et al., 2021; Clarke et al., 2019; Page et al., 2018). Similar negative results were found after applying physical stressors to male mice during early adolescence; although these results were obtained from juvenile animals (Ueno et al., 2018). However, another study, using a combination of physical stressors, found a reduction in the density of these cells in the prelimbic cortex, although only in male mice and not in the infralimbic cortex (Page and Coutellier, 2018). Interestingly, peripubertal CUS increased the dendritic complexity of PV + neurons in the adult mPFC but only in female mice; however, differences in the perisomatic input from PV basket cells on pyramidal neurons were only detected in adult male mice (Bueno-Fernandez et al., 2021). Although we did not find significant changes in the dendritic arborization of PV + interneurons in the mPFC in this experiment (Bueno-Fernandez et al., 2021), a recent report has described that a chronic corticosterone treatment during adolescence significantly reduces the dendritic spine density of both PV+ and SST + interneurons in the hippocampus (Hill et al., 2020).

Using peripubertal CUS with fear-related stressors we also found an important increase in the density of CB1R + perisomatic puncta (coming from CCK + basket cells) on mPFC pyramidal neurons, but only in females and when all animals were analyzed together (Bueno-Fernandez et al., 2021). Similarly, chronic restraint stress in male adolescent rats increased CB1R receptor binding in the mPFC (Lee and Hill, 2013).

Together, these results indicate that the effects of stress during early life can be extremely variable depending on the type of stressor, the age at which they animals are exposed and the sex. There are also different impacts depending on the region studied. During infancy, most reports describe an increase in inhibitory markers in the BLA, but the effects on the cerebral cortex (including the hippocampus) are more heterogeneous. The studies on the stress suffered during adolescence are particularly focused on the PFC and on PV + interneurons. The results on these prefrontocortical interneurons are also variable depending on the sex or the stressor applied. The exploration of other regions of the CNS and other interneuronal populations should be the objective of future studies. In this regard, it is also particularly interesting to analyze the role of cannabinoids, specially in inhibitory synapses, in the response to stress in early life.

3.2.2. Chronic stress during adulthood

Although stress paradigms seem to have a dire effect when exerted during early life, one should not disregard its effects on adult rodents. Models of chronic stress during adulthood include the application of electric foot shocks (Bali and Jaggi, 2015; Dagyte et al., 2009), restraint of the animal (Glavin et al., 1994; Guedri et al., 2017; Martinez et al., 1998; Mumtaz et al., 2018), social stressors that include total isolation and resident-intruder tests (Guedri et al., 2017; Martinez et al., 1998; Mumtaz et al., 2018), and slight modifications of the above. However, when considering chronic stress paradigms, the habituation to these stressors due to their continuous application normally reverts major alterations in the nervous system (Grissom and Bhatnagar, 2009; Herman, 2013). In recent years, new unpredictable stress protocols have emerged to overcome this limitation. These models alternate different stressors performed in an apparently random fashion (Antoniuk et al., 2019; Monteiro et al., 2015).

Even though researchers have oftentimes overlooked the effect of the different chronic stress paradigms on interneurons in the adult brain, recent research has described that they also suffer important alterations. Recent reviews have addressed these changes and linked them to

psychiatric disorders and their treatment, especially major depression (Duman et al., 2019; Prévot and Sibille, 2021).

In the dorsal hippocampus of adult male rats, chronic social isolation for 3 weeks resulted in a reduced number of GAD67+ interneurons in all the subfields (Filipović et al., 2018; Perić et al., 2021). Similarly, the expression of GAD67 protein was decreased in the hippocampus in a 5-weeks CUS paradigm in male rats, although no changes were observed in the expression of other calcium binding proteins or neuropeptides (Banasr et al., 2017). The expression of GAD67 was also reduced in different layers of CA1 and CA3 in male mice subjected to 21 days of restraint (Gilabert-Juan et al., 2017).

Chronic social isolation for 3 weeks in adult male rats also reduces the number of PV + cells in all hippocampal subfields (Filipović et al., 2018; Perić et al., 2021). The number of these interneurons is also lower in the dorsal DG of adult male mice exposed to 14 days of unpredictable mild stress protocol (Chen et al., 2022). In a similar way, in adult male rats exposed to a 7-week mild stress protocol, in which several different stressors were applied (although not in an unpredictable fashion), the expression of PV decreased in the dorsal hippocampus (Rossetti et al., 2018). In addition, rats exposed to protocols of either 14 days of CUS or 8 weeks of chronic mild stress (CMS), presented lower densities of CB expressing interneurons in CA1 and the DG (Nowak et al., 2010). No differences in the number of SST expressing EGFP + cells were detected in adult male GIN mice subjected to 21 days restraint stress (Gilabert-Juan et al., 2017). However, the expression of SST was increased in the dorsal hippocampus of male rats subjected to 7-week of mild stress, although no effect was detected on the expression of NPY or calbindin (Rossetti et al., 2018).

The effects of chronic stress are not restricted only to the modulation of the expression of molecules in interneurons, but also to changes in their structure; the 21-day protocol of restraint stress performed in our laboratory caused a decrease in the complexity of the dendritic arbor of SST expressing interneurons in the *stratum oriens* of dorsal CA1, but not in those of CA3 (Gilabert-Juan et al., 2017). No differences were detected in dendritic spine density in hippocampal SST + cells after this paradigm (Gilabert-Juan et al., 2017).

The interneurons and the molecules related to inhibitory neurotransmission of the amygdala are also affected by chronic stress (see (Jie et al., 2018) for review). A model of 21 days of restraint stress performed in our laboratory led to a decrease in the expression of GAD67 in the medial amygdaloid nucleus of male mice (Gilabert-Juan et al., 2011). By contrast, a 10-day model of restraint stress caused an increase in the number of PV + interneurons in the BLA of adult male rats (Pesarico et al., 2019). In this same amygdaloid nucleus, a protocol of sensory contact stress of 10 min performed during 10 consecutive days, showed that subordinate mice displayed a lower density of PNNs and a trend towards a decrease in the density of PV expressing cells covered by PNNs (García-Mompó, unpublished results). In addition, the structure of SST + cells was also affected by 21 days of chronic stress in adult male mice: the complexity of their dendritic arbor was decreased (Gilabert-Juan et al., 2011), opposite to the results that have classically been described in pyramidal neurons.

The PFC cortex is also an important target of chronic stress during adulthood. In fact, several stress paradigms have shown alterations in inhibitory systems in this region. Different reviews have analyzed GABAergic dysfunction in the PFC after adverse experiences and major depression (Fogaça and Duman, 2019; McKlveen et al., 2019). In male rats, GABA levels were reduced by CMS (Shalaby and Kamal, 2009), while repeated restraint stress caused this reduction along with an increase in the activation of GAD and GABA turnover (Otero Losada, 1988). Likewise, a 9-week CMS paradigm caused reductions of GABA release, sIPSC frequency and GABAB receptor inhibition, in the mPFC of anhedonic male rats (Czéh et al., 2018). Different chronic stress paradigms, including CUS and CMS, decreased GABAergic innervation and the expression of GAD67, VGAT, and GABA plasma membrane transporter-3 (GAT3) in the PFC (Banasr et al., 2017; Gilabert-Juan et al., 2013b; Ma et al., 2016).

In our laboratory we have described an increase in the number of PV expressing interneurons in the mPFC of male rats exposed to chronic restraint stress for 10 days (Pesarico et al., 2019). An unpredictable CMS protocol performed for 4 weeks also caused an increase in the number of active PV + interneurons in the mPFC of both male and female mice (Page et al., 2019; Shepard and Coutellier, 2018). However, in the orbitofrontal cortex of adult male rats a similar, but longer, 7-week protocol did not produce alterations in the number of PV + cells (Varga et al., 2017). A 9-week CMS model caused a decrease in the numbers of PV+ in the infralimbic cortex of anhedonic male rats (Czéh et al., 2018), while 8 weeks of this protocol or 14 days of CUS caused no changes in the density of prefrontocortical PV + cells of adult male rats (Zadrożna et al., 2011). This same report also described that there were no changes in the density of these cells after a 2-week CUS protocol. However, the length of the model and the sex analyzed seem to be of paramount importance on the effects of chronic stress on inhibitory circuits: The number of PV + interneurons in the PFC was increased after a 2-week CUS paradigm, while the results returned to control levels if the protocol lasted 4 weeks in adult female but not male mice (Shepard and Coutellier, 2018). In another CUS paradigm, performed for 5 weeks, the expression of PV protein was also decreased in the PFC (Banasr et al., 2017).

SST expressing interneurons are also affected by different stress protocols. Although their number remained unaffected in the orbitofrontal cortex of adult male rats subjected to a 7-week CUS protocol (Varga et al., 2017) as a whole (Banasr et al., 2017). The structure of SST + cells was also affected by chronic stress, a 3-week protocol of CMS performed in our laboratory led to an increase in the complexity of their dendritic arbor in adult male mice (Gilabert-Juan et al., 2013b).

Other types of interneurons were also susceptible to change after different chronic stress paradigms. A 7-week CUS produced a marked reduction of CB + cells, but no alterations in CR, cholecystokinin or NPY expressing interneurons in the orbitofrontal cortex of adult male rats (Varga et al., 2017). Likewise, 9 weeks of CMS caused a decrease in the number of CR + interneurons in the infralimbic cortex, while CCK + interneurons were also decreased in the prelimbic and cingulate cortices of anhedonic male rats (Czéh et al., 2018). The density of CB + interneurons was differentially affected depending on the stress protocol performed. In adult male rats, 14 days of CUS led to a decrease, whereas a 8-week CMS protocol caused an increase in the density of these cells in the PFC (Zadrożna et al., 2011). In another CUS paradigm, performed for 5 weeks, the expression of CB and CR protein remained unaffected, while the mRNA expression of NPY was decreased in the PFC of adult male rats (Banasr et al., 2017).

Most of the studies of the effects of stress on inhibitory neurons have been focused on the three classical regions involved in mood disorders: hippocampus, amygdala and PFC. However, molecules related to inhibitory neurotransmission and interneurons of other regions have also been implicated and affected in different stress paradigms. Such is the case of the ventromedial medulla and locus coeruleus, part of the descending pain modulatory system. Here, 3 weeks of chronic restraint stress led to higher GAD67 protein levels, and higher number of GABAergic neurons that had been acetylated on histone H3 in the ventromedial medulla of repeated restrained male rats (Imbe and Kimura, 2018). On the other hand, regions related to the reward system have also recently gathered some attention. An RNA-seq study of the ventral tegmental area performed on male mice exposed to chronic social defeat stress for 10 days (combining emotional and physical stress groups) showed that genes related to GABAergic signaling were overexpressed in this region (Tao et al., 2021; Warren et al., 2013). Another 10-day chronic social defeat stress model using the resident-intruder test showed that mice susceptible to stress presented a lower density of puncta expressing VGAT, and both susceptible and resilient mice exhibited higher mRNA expression of this transporter in the nucleus accumbens. In addition, only resilient mice showed a higher density of

puncta expressing the inhibitory postsynaptic scaffold protein gephyrin, with no changes in its mRNA expression (Heshmati et al., 2020). In this same region, a similar protocol showed that there were no alterations in the number of D2-medium spiny neurons or ChAT interneurons in either susceptible or resilient male mice (Chandra et al., 2017). Lastly, lateral habenula has also been shown to be highly related to stress response in relation to the reward system (Nuno-Perez et al., 2021; Proulx et al., 2014; Shabel et al., 2019). Here, another 10-day resident-intruder study showed that susceptible male mice presented lower GABA(B1) and GABA(B2) relative densities in the lateral habenula (Li et al., 2021). Also in the diencephalon, 10 days of restraint stress produced a decrease in the density of PV + cells in the thalamic reticular nucleus (TRN) (Pesarico et al., 2019).

As it happens with chronic stress during early life, the effects of this adverse experience during adulthood on inhibitory circuits are also dependent on the type of stressor, its duration, and the sex and species under study. Although most reports point to a decrease in inhibition, there is a need for more detailed studies on specific interneuronal populations and for agreements to define standard models in which focus many studies, to get more accurate views. An important problem in the field is the high variability between studies in terms of the type of stressors and their duration or even in the age of animals used. This makes comparisons complicated, because stress may induce a different response of inhibitory circuits depending on these factors. The sex is also an important issue, because to date relatively few studies have focused on females. This is particularly worrying because women represent half of the human population, some of the stress related psychiatric disorders are more prevalent in them and it is becoming clear that the response to stress is different depending on the sex of the individual. Many investigations have been carried out in the PFC and future studies should expand what is already known in the amygdala and hippocampus. These studies should also start to explore other regions, especially those suggested by alterations in neuroimaging studies in patients suffering from disorders in which stress is a predisposing factor. Another important issue, which will require further research is the influence of aging in the response of the inhibitory circuits to stress. To date, most, if not all, studies have focused on young adult animals.

3.3. *Effects of stress on molecules related to interneuronal plasticity*

In this section we focus on how stress impacts the expression of different neuronal plasticity molecules, with a particular focus on those involved in the inhibitory circuits of the limbic system.

Neuronal structural plasticity is known to have a major role in cognitive processes and in the response of the central nervous system (CNS) to aversive experiences. Structural plasticity involves processes ranging from neurite outgrowth/retraction or dendritic spine remodeling, to the incorporation of new neurons to the established circuitry. However, the study of how these changes take place has been focused mainly on excitatory neurons, while little attention has been paid to interneurons. The exploration of these plastic phenomena in interneurons is very important, not only for our knowledge of CNS physiology, but also for understanding better the etiology of different psychiatric and neurological disorders, in which alterations in the structure and connectivity of inhibitory networks have been described.

3.3.1. *The polysialylated form of the neural cell adhesion molecule*

Different molecules may mediate the structural plasticity of interneurons, especially those involved in cell adhesion or cytoskeletal dynamics. As we mentioned in the first chapter of this review, PSA-NCAM is one of them, in which we have particularly worked in the last years. NCAM has the ability to incorporate long polymeric chains of the sugar sialic acid, which are negatively charged and highly hydrated, thus producing a steric impediment for homotypic and heterotypic interactions (Rutishauser, 2008). The anti-adhesive properties of PSA-NCAM facilitate structural plasticity in the CNS (Bonfanti, 2006; Gascon et al., 2007; Rutishauser, 2008). Another non-excluding role of PSA-NCAM may be the partial synaptic insulation of neuronal elements (Gómez-Climent et al., 2011). During embryonic development there is a massive and widespread expression of PSA-NCAM, which mediates cell migration, neurite outgrowth and synaptogenesis. Postnatally, PSA-NCAM expression is dramatically reduced, but it is still present in some regions of the adult CNS. In these regions, the presence of PSA-NCAM has been related to neurogenesis and, in fact, this molecule is expressed by immature neurons in the neurogenic regions of the adult brain and the cortical layer II (Bonfanti and Nacher, 2012; Seki and Arai, 1993). Due to this intense expression in immature neurons, PSA-NCAM has been erroneously considered in many studies an exclusive neurodevelopmental marker. But PSA-NCAM expression has been described in mature neurons in different neocortical regions, the hippocampus (outside the subgranular zone), the septum and the amygdala (Bonfanti, 2006; Foley et al., 2003; Nacher et al., 2002a; Nacher et al., 2002b). Similar PSA-NCAM expression patterns have been observed in the neocortex, the amygdala, hippocampal formation and entorhinal cortex of humans (Emilio ; Alcaide et al., 2019; Emilio; Arellano et al., 2002; Mikkonen et al., 1998; Varea et al., 2007b; Varea et al., 2012). Work from our laboratory has demonstrated that most, if not all, these mature neurons are in fact GABAergic cells, both in rodents (Juan ; Gómez-Climent et al., 2011; Nacher et al., 2002a; Varea et al., 2005) and in humans (Emilio ; Varea et al., 2007b; Varea et al., 2012). PSA-NCAM has a crucial role in the regulation of the structure and connectivity of these interneurons, particularly of PV+ and SST + cells (Castillo-Gómez et al., 2008, 2011, 2016; Gómez-Climent et al., 2011; Guirado et al., 2014a; Nacher et al., 2013).

Given the relevant role that PSA-NCAM has on the plasticity of adult neuronal circuits and particularly on inhibitory neurons, we started, in collaboration with Bruce, studies directed to understand how stress can affect the expression PSA-NCAM. However, the first study on how stress affected PSA-NCAM expression was published by Carmen Sandi's group in 2001, showing that chronic restraint in adult male rats decreased hippocampal PSA-NCAM expression (Sandi et al., 2001). Using a similar paradigm we found a biphasic expression pattern, but focusing only in the DG (Pham et al., 2003). From there different studies have explored the effects of stress, both during adulthood and early life, on PSA-NCAM expression in different cerebral regions (J. ; Juan ; Cordero et al., 2005; Nacher et al., 2004a; Nacher et al., 2004b; Tsoory et al., 2008), (see Bisaz et al., 2009; Sandi, 2004) for review). In 2011 and 2013, we published 2 articles studying these effects in adult male mice exposed to 21 days of restraint. We found a reduction of PSA-NCAM at the protein and mRNA levels in the amygdala (Gilabert-Juan et al., 2011), but no changes were detected in the mPFC (Gilabert-Juan et al., 2013b). Later on we also observed that this chronic stress paradigm did not change PSA-NCAM expression in the hippocampus (Gilabert-Juan et al., 2017). More recently we have performed a 10-day restraint stress model on adult male rats and studied its effects on the CA1 of the dorsal and ventral hippocampus, the mPFC and the BLA. Here we have found increases in the relative expression of PSA-NCAM in the stratum lacunosum moleculare of the dorsal hippocampus, while these increases were located in the strata pyramidale and radiatum when studying the ventral hippocampus, with no alterations in the other regions studied (Pesarico et al., 2019).

Some years later, we became interested in the effects of stress during brain development and their link to neuropsychiatric disorders. We found that male rats reared in isolation (from P21 until adulthood) had a reduced expression of PSA-NCAM in the BLA (Gilabert-Juan et al., 2012a), but not in the mPFC or the hippocampus (Gilabert-Juan et al., 2013a). This same postweaning isolation stress also reduced PSA-NCAM expression in the whole amygdala in male mice (Castillo-Gómez et al., 2017). In that same line of work, we have recently used a peripubertal CUS model and found that stressed male and female mice displayed an increased number of PSA-NCAM expressing interneurons in the infralimbic region of the adult mPFC (Bueno-Fernandez et al., 2021).

Previous work using a similar peripubertal CUS in male rats found reduced GAD expression in different PFC regions and a decrease in neuroligin-2 specifically in the prelimbic cortex (Tzanoulinou et al., 2016). This stress model also reduced GAD and GABA-A alpha3 receptor expression in most amygdaloid nuclei (Tzanoulinou et al., 2014).

3.3.2. Perineuronal nets

The plasticity of interneurons is also regulated by components of the extracellular matrix, in particular by dense and specialized regions: the PNNs. A trait of many PV + cells is the coverage of their somata and proximal dendrites by these structures, which display a lattice-like morphology (Celio et al., 1998). PNNs are formed during development (Brückner et al., 2000) in an activity-dependent manner (Dityatev et al., 2007). These structures are composed of hyaluronan, chondroitin sulfate proteoglycans (CSPG), tenascins and link proteins in different ratios and region-specific compositions (Fawcett et al., 2019; Ueno et al., 2018). The appearance of PNNs surrounding PV + cells marks an abrupt reduction of neuronal plasticity at the end of the critical periods, temporal windows of enhanced neuronal plasticity that occur during the latest stages of development (Hensch, 2005). The PNNs have an important role in the maturation and stabilization of the connectivity of PV + interneurons in critical periods such as those of the visual and auditory systems (Cisneros-Franco and de Villers-Sidani, 2019; Pizzorusso et al., 2002), and in the development of traits governed by the limbic system, such as the development of anxious behaviors (Vincent et al., 2021). As in the case of PSA-NCAM, we and others have investigated the influence of stress on PNNs and their relationship with the structural plasticity of inhibitory neurons, particularly, with that of PV + interneurons.

Several studies indicate that early life stress, specifically during the critical periods, can affect the development of the PNNs in different brain areas. Male mice subjected to repeated maternal separation and early weaning display increased intensity of PNNs in the ventral hippocampus (Murthy et al., 2019).

The effects of early life stress in the BLA have led to controversial results, accelerating or delaying the maturation of the PNNs depending on the age, the sex, the species of rodent or the type and duration of stressor. Gildawie et al. (2020), using repeated maternal separation in rats (4h per day from P2–P20), observed an increase in the density of PNNs in the BLA of adolescent males. By contrast, Richardson et al. (2021) failed to replicate these findings, with a slightly different protocol of maternal separation (3h per day from P2–P14) in male and female rats (Richardson et al., 2021). Using a limited bedding and nesting paradigm, which causes disruption of maternal care, male but not female adolescent rats presented an increased density of PNNs in the right BLA (Guadagno et al., 2020). Conversely, a similar limited bedding stressor, in male and female rats considered together, did not induce changes in the density and intensity of the PNNs in this amygdaloid nucleus (Santiago et al., 2018). While we also failed to observe changes in the density of PNNs in different amygdaloid nuclei of adult male mice subjected to postweaning social isolation (Castillo-Gómez et al., 2017), we found that the same animal model increased the density of PNNs in the BLA in rats (Mikics et al., 2018), an alteration that, as we will discuss below, can be reversed by antidepressants.

Maternal separation delays the formation of PNNs in the prelimbic region of the mPFC both in male and female rats, but only during youthhood: changes are lost in adolescence and adulthood. This effect is also seen in the infralimbic region, but persists until adulthood (Gildawie et al., 2020). By contrast, repeated maternal separation followed by postweaning social isolation reduces the intensity of PNNs in the prelimbic and infralimbic regions of the mPFC in female but not in male rats (Gildawie et al., 2021). In male adolescent rats subjected to CUS, an increased number of PNNs was observed in the whole mPFC after 7 days of stress, but this number decreased 35 days after (Folha et al., 2017). Our analysis of adult male and female mice subjected to peripubertal CUS (48 days after the stress) did not reveal any changes in PNNs in the infralimbic mPFC (Bueno-Fernandez et al., 2021). Regarding the percentage of PV expressing cells covered by PNNs in the adult PFC of rodents subjected to peripubertal stress, most studies in mice did not find differences (Bueno-Fernandez et al., 2021; Page and Coutellier, 2018; Ueno et al., 2018). By contrast, postweaning social isolation increased the number of PV + interneurons surrounded by PNNs in the mPFC (Castillo-Gómez et al., 2017).

The impact of stress on PNNs has been recently reviewed (Laham and Gould, 2021; Spijker et al., 2020). Social defeat–induced persistent stress reduced the number of PNNs in the hippocampus of adult male rats when observed 72 h after this adverse experience, but increased it when observed 8 weeks after (Koskinen et al., 2020; Riga et al., 2017). A similar increase in PNNs was observed in the whole cerebral cortex of adult male mice after 35 days of chronic variable stress (Simard et al., 2018). Conversely, PNNs density was reduced in hippocampal CA1 region after 10 days of chronic restraint stress protocol, but increased in the mPFC (Pesarico et al., 2019). No changes were observed in the BLA, but increases were found in the habenula and the TRN (Pesarico et al., 2019).

4. Reversion of effects of stress on interneurons: antidepressants and enriched environment

As discussed above, it has been long thought that stress, especially during early life, is one of the main predisposing factors for neuropsychiatric disorders due to its impact on neuronal plasticity. Fortunately, different interventions can attenuate or revert these adverse effects of stress. Here we evaluate how they can be reversed through experimental manipulations, such as the administration of antidepressant drugs or the use of environmental enrichment.

The direct manipulation of GABAergic neurotransmission, through selective allosteric modulators of GABAA receptors containing alpha5 subunits, can rescue depressive- and anxiety-like behaviors in rodent stress models. Surprisingly, this can be achieved using positive (Piantadosi et al., 2016) and negative (Fischell et al., 2015) modulators and, at least in the case of the positive modulators it is only effective in females (Piantadosi et al., 2016). It is also interesting to mention that brenaloxone, a positive allosteric modulator of GABAA receptors, has shown promising potential as an antidepressant in patients suffering from postpartum depression (Morrison et al., 2019).

In this context, it is important to note the contrasting patterns that stress exerts on different parts of the rodent brain, particularly between the hippocampus and the amygdala in many of the parameters considered in this review, especially those concerning GABA, as we have described in the previous sections above. In this same line, most chronic stress models induce dendritic atrophy and loss of spines in excitatory neurons of the hippocampus (Magariños and McEwen, 1995; Mychasiuk et al., 2012; Sousa et al., 2000; Watanabe et al., 1992), while they produce the inverse effect in the amygdala (Vyas et al., 2002). Importantly, these changes can be reversed by antidepressants, such as fluoxetine (Magariños et al., 1999), a well-known serotonin selective reuptake inhibitor, by promoting an increase in spine density of pyramidal neurons in the hippocampus (Guirado et al., 2009; Hajszan et al., 2005).

Stress also produces a decrease in BDNF expression in the hippocampus of adult male rats, while it leads to an increase in the amygdala (Lakshminarasimhan and Chattarji, 2012), suggesting an important role for this neurotrophin in the structural changes observed. Furthermore, in humans, a common polymorphism in the BDNF gene, the substitution of Val to Met at codon 66, known as Val66Met, (Shimizu et al., 2004), has been associated with some neuropsychiatric disorders (Harrisberger et al., 2015). Interestingly, this polymorphism linked to stress also causes reduced structural features in both PV+ and SST + hippocampal interneurons in male and female mice (Hill et al., 2020). By contrast, fluoxetine and other antidepressants increase the expression and signaling of neurotrophic factors, including BDNF (Larsen et al., 2008;

Nibuya et al., 1995; Russo-Neustadt et al., 2000; Saarelainen et al., 2003). As mentioned above, in our laboratory, we have reported that SST expressing interneurons in the mPFC of chronically stressed male mice showed reduced dendritic arborization (Castillo-Gómez et al., 2015). We have shown that in this same subpopulation of interneurons and in the same brain region, the antidepressant fluoxetine increased dendritic spine density (Guirado et al., 2014b). Chronic fluoxetine treatment altered significantly the expression of PSA-NCAM in different regions of the brain (Guirado et al., 2014, 2012; b; Varea et al., 2007a; Varea et al., 2007c), including those classically affected by stress and may revert the effects of this adverse experience. This antidepressant also altered the number of PV + neurons surrounded by PNNs in the mPFC and hippocampus of adult male mice (Guirado et al., 2014b). Unfortunately, experiments combining stress with fluoxetine to study these molecules related to interneuronal plasticity are still scarce. Nevertheless, through BDNF and TrkB signaling, fluoxetine induced an increase in neuronal plasticity that did not only reverse the effects of stress on the expression of plasticity markers, such as PSA-NCAM or the ratio of PV + interneurons surrounded by PNNs, but also reopened a critical period that allows experience to affect different behaviors related to the limbic system such as aggression (Mikics et al., 2018) and fear (Karpova et al., 2011).

Different studies have shown that the effects of chronic stress on the total number and density of PV + interneurons (Perlman et al., 2021) can be reversed by different pharmacological treatments, especially by antidepressants. Treatment with fluoxetine normalized the decrease in the number of PV + interneurons in adult tree shrews submitted to 5 weeks of psychosocial stress in the different regions of the hippocampus (Czeh et al., 2005). Fluoxetine and the antipsychotic clozapine, when administered during 3 weeks of social isolation in adult male rats, also offered protection from the isolation stress-induced reduction in the number of PV + interneurons in hippocampal subregions (Filipović et al., 2018). The reduction of the number of PV + interneurons in the dorsal hippocampus after chronic social isolation in adult male rats could also be prevented by treatment with tianeptine, an atypical antidepressant from the group of selective serotonin reuptake enhancers. Consequently, the authors suggested that tianeptine may protect from stress via the modulation of the dorsal hippocampal GABAergic system (Perić et al., 2019). Electrophysiological and *in vivo* imaging experiments have shown that ketamine increased PV + interneuron activity and prevented net loss of PV + axonal boutons under stress conditions (Ng et al., 2018). However, there are studies that have failed to observe these protective effects of antidepressants on the loss of PV + cells. For instance, after CMS in adult male rats, escitalopram (another serotonin reuptake inhibitor) reversed anhedonic behavior, but did not affect the alterations in the number of PV + interneurons (Nieto-Gonzalez et al., 2015).

Antidepressants, such as fluoxetine, as mentioned before, also increased the expression of PSA-NCAM (Carceller et al., 2018; Guirado et al., 2014b), and the decrease of PSA-NCAM expression induced by acute stress could be blocked by the use of a different antidepressant, agomelatine (Conboy et al., 2009).

We and others have also observed these seemingly opposite effects of stress and antidepressants when studying the presence of PNNs surrounding PV + neurons. Similar decreases have been observed in the mPFC and the hippocampus after early-life stressful experiences, such as rearing in social isolation, both in male mice (Castillo-Gómez et al., 2017) and rats (Mikics et al., 2018), and treatment with fluoxetine could revert these changes in PNN density (Mikics et al., 2018). Interestingly, the enzymatic remodeling of the hippocampal extracellular matrix is able to restore the deficits in PNNs, LTP maintenance, hippocampal inhibitory tone, and cognitive impairment induced by chronic social defeat–induced stress (Riga et al., 2017).

Recently, new drugs known to promote brain plasticity are being considered as fast-acting antidepressants, including psilocybin, ketamine and isoflurane. All these are potential therapeutic compounds to ameliorate the effects of stress on the brain, since one of these effects appears to be the constriction of brain plasticity (Castrén, 2005). Both clinical and animal studies demonstrated that a single dose of ketamine provoked anti-depressant effects (Autry et al., 2011; Berman et al., 2000; Li et al., 2010). In this line, ketamine disrupted the inflammation associated with repeated social stress in adult rats (Moraga-Amaro et al., 2022) and blocked the acute stress-induced enhancement of glutamate release at different time-points after a footshock in adult rats (Sala et al., 2022). Ketamine also rescued the dendritic retraction of pyramidal neurons induced by acute stress in the PFC (Sala et al., 2022). These structural changes are likely due to the effects of ketamine on GABAergic neurons, since a single dose of this drug not only reversed CUS-induced deficits in the expression of GABA-related molecules and depressive-like behaviors (Ghosal et al., 2020), but also suppressed the activity of SST expressing interneurons, leading to greater synaptically evoked calcium transients in the apical dendritic spines of pyramidal neurons in the PFC (Ali et al., 2020). Furthermore, ketamine increased PNNs in the PFC of mice submitted to CUS and neurocan, one of components of these extracellular matrix structures, mediates the effects of ketamine on depressive-like behavior (Yu et al., 2022). Interestingly, these antidepressant effects of ketamine were blocked by the specific knockdown of the GluN2B NMDAR subunit in GABAergic interneurons of the mPFC (Gerhard et al., 2020).

Physical exercise and environmental enrichment, a method of enhanced cognitive, sensory and motor stimulation, could decrease the deleterious effects of stress on PV + cell structure and function. Running and environmental enrichment, reverted the stress-induced electrophysiological reduction of activity of PV expressing interneurons produced by stress (Chen et al., 2018; Lehmann and Herkenham, 2011). Running exercise has a positive effect on depressive-like symptoms induced by stress. Two weeks of running increased the expression of PGC-1α, a transcriptional coactivator, in the hippocampus of mice exposed to chronic unpredictable stress (Wang et al., 2021). Because PGC-1α is closely related to PV + interneuron function (Lucas et al., 2014), the authors hypothesized that this exercise could regulate it to reverse depressive-like behaviors.

Male and female mice subjected to CUS during early life, but raised in an enriched environment, did not experience the stress-induced reduction in the activity of PV + interneurons (Chen et al., 2018), similar to other studies suggesting that environmental enrichment promoted resilience to stress (Lehmann and Herkenham, 2011). Environmental enrichment in aged rats (24h/day over a period of 2 months) increased the density of PV + cells in prefrontal regions and reverted the detrimental effects of cat odor stimuli (Sampedro-Piquero et al., 2016). Environmental enrichment also reversed the down-regulation of PV expression in the hippocampus and PFC of adult male rats induced by inescapable foot shocks (Sun et al., 2016).

In summary, this review clearly demonstrates that stress also has an important impact on inhibitory circuits and highlights the need of expanding its research to deepen in the knowledge of the consequences that adverse experiences produce in our brain. In this regard, different issues seem particularly interesting for future investigations. Longitudinal studies should dissect whether the stress-induced changes in inhibitory neurons are prior, simultaneous or the consequence of previous alterations in excitatory neurons. Sex is also a crucial factor to understand the consequences of stress: future research in animal models and humans should include always females and explore in detail why there is a differential vulnerability to stress and stress-related disorders. The period of life in which stress occurs is also a very important factor for the response of inhibitory circuits. The consequences of stress during early life should be particularly explored, because many psychiatric disorders in which early stress is a precipitating factor show alterations in their inhibitory networks. Investigations should also focus on molecules that control the neurochemistry and plasticity of interneurons, in order to develop new drugs directed to alleviate or prevent the consequences of stress. Many questions remain open and many others will

surely emerge in the future. We are also sure that, without the enormous contribution of Bruce McEwen many of these questions could not even be asked.

CRediT authorship contribution statement

Marta Perez-Rando: Writing – review & editing, Visualization. **Hector Carceller:** Writing – review & editing. **Esther Castillo-Gomez:** Writing – review & editing. **Clara Bueno-Fernandez:** Writing – review & editing. **Clara García-Mompó:** Writing – review & editing. **Javier Gilabert-Juan:** Writing – review & editing. **Ramón Guirado:** Writing – review & editing. **Ana Paula Pesarico:** Writing – review & editing. **Juan Nacher:** Supervision, Writing – review & editing.

Declaration of Competing interest

The authors of the manuscript "Impact of stress on inhibitory neuronal circuits, our tribute to Bruce McEwen" declare that they do not have conflicts of interest.

Acknowledgements

This work was supported by the projects RTI2018-098269-B-I00 and RTI2018-095698-B-100 financed by the Spanish Ministry of Science and Innovation/AEI/10.13039/501100011033/("FEDER Una manera de hacer Europa"), the Generalitat Valenciana (PROMETEU/2020/024 and AICO/2021/246), Universidad Autónoma de Madrid - Comunidad Autónoma de Madrid, Programa de estímulo a la investigación de jóvenes doctores (Project SI3-PJI-2021-00417) and Universitat Jaume I de Castelló, Plà de Promoció a la Investigació (UJI-A2020-20). HC is supported by a postdoctoral "Margarita Salas" grant from the Universitat de València funded by the Spanish Ministry of Science and the Next Generation EU. MP-R is supported by a postdoctoral "Atraccio de Talent" grant from the Universitat of Valencia. CG-M is supported by a postdoctoral grant from the Universitat Jaume I.

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