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Do changes in microglial status underlie neurogenesis impairments and depressive-like behaviours induced by psychological stress? A systematic review in animal models

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ABSTRACT

Stress may have a negative effect on mental health and is the primary environmental risk factor in the aetiology of depression. Nevertheless, the neurobiological mechanisms underlying this mood disorder remain poorly characterized. The hippocampus is a target structure of the adverse effects of stress, and hippocampal neurogenesis plays a crucial role. However, we do not know the mechanisms by which stress impacts neurogenesis. Recent studies indicate that changes in neuroinflammation, primarily via microglial cells, may play an essential role in this process. However, the relationship between stress, microglial changes, and alterations in neurogenesis and their involvement in the development of depression is poorly characterized. For this reason, this systematic review aims to synthesise and evaluate current studies that have investigated the relationship between these variables. Taken together, the revised data, although not entirely conclusive, seem to suggest that microglial changes induced by psychological stress regulate neurogenesis and in turn may be responsible for the development of depressive-like behaviours, but other factors that influence these stressful experiences should not be dismissed.

1. Introduction

Stress, particularly chronic stressful life events, may have a negative impact on mental health, and is the primary environmental risk factor in the aetiology of depression, a prevalent disease with devastating consequences. In fact, depression is currently a leading cause of disability worldwide and one of the major factors contributing to the overall global load of disease (World Health Organization, 2020).

Nevertheless, the neurobiological mechanisms underlying this mood disorder remain poorly characterized. Along with other regions, the hippocampus is a target structure of the adverse effects of stress. It is directly involved in endocrine responsiveness (McEwen, 2003; Snyder et al., 2011) and indirectly related to immune responses (McEwen, 2003) and emotional and motivational impairments that are central symptoms of depression (Jöels et al., 2011).

Cellular disturbances at the hippocampal level have been linked to the neuropathology of mood disorders (Sahay and Hen, 2007; Schmidt and Duman, 2007; Warner-Schmidt and Duman, 2006; Lino de Oliveira et al., 2020), particularly impaired neurogenesis (Campbell et al., 2004; Lucassen et al., 2010; Snyder et al., 2011). Several studies have revealed that stress strongly suppresses adult hippocampal neurogenesis. Both acute and chronic stress have been reported to decrease adult neurogenesis by reducing both neuroprogenitor proliferation and new-born cell survival (Ito et al., 2017; Lu et al., 2014; Schoenfeld and Gould, 2012), as well as impairing new-born neuron maturation (Lee et al., 2019; Llorens-Martín et al., 2016). In this sense, it has been observed that neurogenesis may be involved in buffering the negative effects of stress; however, decreased adult neurogenesis, in contrast, may lead to enhanced responsiveness to future stress (Snyder et al., 2011). With some exceptions, reductions in neurogenesis combined with a genetic predisposition or an environmental insult, such as stress, result in depression (Sahay and Hen, 2007). Although the mechanism is not

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entirely clear, this neurogenic impairment may explain, at least in part, reduced hippocampal volumes, which is likely the most common structural neuroimaging finding observed in major depressive disorder (MDD) (Bremner et al., 2000; Hickie et al., 2005; Sheline et al., 1999, 2003; Szymkowicz et al., 2019).

However, precisely how stress impacts neurogenesis remains unknown. Recent studies indicate that changes in neuroinflammation, mediated primarily via microglial cells, may play an essential role in this process. In this sense, numerous inflammatory processes that can be triggered by external viral or bacterial pathogens (Miller and Raison, 2016; Vollmer-Conna et al., 2004), or by immunotherapy for certain types of cancer or hepatitis C with interferon-, promotes microglial activation (Cho et al., 2020; Raison et al., 2006) and has been associated with depression (Gale et al., 2018). Microglia comprise approximately 10–15% of all cells in the brain and are the cells responsible for organizing the brain's innate immune response (reviewed in Sierra et al., 2010). Among their numerous functions, microglia play a role in regulating adult neurogenesis (Díaz-Aparicio et al., 2020; Ekdahl et al., 2003; Kempermann and Neumann, 2003; Sierra et al., 2010; Valero et al., 2016). Thus, microglia may modulate adult neurogenesis through several mechanisms: surveillance of the neurogenic niche, phagocytosis of apoptotic new-born cells (Díaz-Aparicio et al., 2020; Sierra et al., 2010), release of pro-neurogenic soluble factors (Valero et al., 2016) and maintenance of baseline neurogenic cascade homeostasis (Sierra et al., 2010). Under pathological conditions, such as high levels of emotional stress, the neuroendocrine response to stress rises rapidly increases levels of glucocorticoids (De Kloet al., 2008, Hunter et al., 2016). Microglia express glucocorticoid receptors and exhibit changes in morphology, density and release of cytokines into the hippocampus, which may in turn affect neurogenesis (Valero et al., 2016). Thus, microglial activation under stressful conditions may be a key mechanism of neurogenesis suppression (Ekdahl, 2012; Kempermann and Neumann, 2003). Stress induces a concomitant effect on both adult neurogenesis and microglia (Valero et al., 2016). Nevertheless, while most studies have provided evidence for the involvement of microglial activation in depression, other studies suggest that rather than activation, decreased microglial activation or even microglial atrophy, occur with a reduction in the inflammatory status, which may be linked to impaired neurogenesis and, in turn, to depression (Carboni et al., 2010; Yirmiya et al., 2015). These results point to a more complex scenario of microglial dynamics after stress, but it remains unclear why stress may induce both increased activation and microglial atrophy.

Based on current preclinical evidence, it is hypothesized that microglial changes in the hippocampus depend on stress and may induce neurogenesis impairment and, in turn, depressive-like behaviours. However, while clear associations between stress and depression (Calcia et al., 2016; Dutcher et al., 2020), stress and neurogenesis (Brunoni et al., 2008; Vollmayr et al., 2007; Lino de Oliveira et al., 2020), stress and microglial changes, microglia and neurogenesis (Díaz-Aparicio et al., 2020; Sierra et al., 2010; Valero et al., 2016) and microglia and depression (Calcia et al., 2016; Dutcher et al., 2020) have been established, fewer studies have evaluated the association among all four of these components collectively. For this reason, the objectives of this systematic review were to (a) identify which depressive symptoms are induced by psychological stress; (b) identify neurogenesis impairments induced by stress; (c) assess microglial changes in the hippocampus produced by psychological stress; (d) discuss why depression has been linked to both increased and decreased microglial activation; (e) determine which inflammatory molecules, primarily hippocampal cytokines, are related to microglial changes induced by stress; and finally, (f) evaluate whether stress-associated microglial and/or neuroinflammatory changes correlate with neurogenesis impairments and with depressive-like behaviours in animal models. This systematic review may provide insight into the neurobiological mechanisms underlying depression induced by stress based on changes in microglial status and neurogenesis.

2. Methods

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic review of animal model studies examining the effect of psychological stress on microglial and neurogenic changes in the development and/or progression of depressive symptoms was conducted. This review protocol was registered at the PROSPERO website on November 16th, 2020 under review number CRD42020207364.

2.1. Search strategy

Studies were identified by searching PubMed, Medline, Web of Science, EMBASE, SCOPUS and Google Scholar (200 first references (Bramer et al., 2017)) from inception to July 2020 using the following search terms: "stress and/or variants" AND "microglia" or variants AND "neurogenesis or stem cells or new-born cells or neural or neuronal survival" or variants AND "depression or depression-like behaviour or mood disorder" and variants. Thus, search terms were kept consistent for all databases and were modified only by truncating characters when required. Additional relevant articles were identified by a manual search of article reference lists. The articles were reviewed for inclusion by two independent researchers (A.N-Q. and P.C–P.). Disagreements between reviewers were resolved via consensus or arbitration by third and fourth reviewers (M.P-M. and C.P., respectively).

Psychological stress was defined to include a broad range of stressors distinguishing between early life stress (maternal separation (MS), maternal sleep deprivation (MSD) and adult stress (chronic unpredictable mild stress (CUMS), chronic social defeat stress (RSDS), chronic water immersion restraint stress (CWIRS), sleep deprivation (SD)). Microglial changes were broadly defined to include any valid indicator of microglial activity change (e.g., modification in number, soma changes, prolongation changes, changes in inflammatory molecules). These changes have focused on the hippocampus. Neurogenic changes were included in studies that used classic tools for detecting and quantifying neurogenesis, such as thymidine analogues as exogenous markers of DNA replication or newly generated cells in the adult brain, markers for endogenous cell cycle proteins that are expressed at different stages of cell cycle progression or markers of transitory lineage commitment stages before adoption by new-born cells of a mature phenotype. Finally, to study the effects on depression, behavioural tests that replicated depression-like symptoms were considered (e.g., the sucrose preference test (SPT), the forced swimming test (FST), the tail suspension test (TST), social interaction tests, etc.).

2.2. Eligibility criteria

Studies were selected based on the following inclusion criteria: 1) original research, 2) published in a peer-reviewed journal, and 3) written in English. The studies were required to include a valid measure of microglial and neurogenic change that was associated with an environmental stressor and at least one of the measures of depression-like behaviours in animal models (e.g., anhedonia, helplessness, cognition, etc.). For this reason, only studies performed 'in vivo' were included.

2.3. Data extraction

Data extraction was performed by A.N-Q. and P.C–P. using a custom-made form to assess the methods and outcomes of the studies. The data were stored in a MS Excel spreadsheet. For each study, the following variables were recorded: (a) master record number, (b) year of publication, (c) authors, (d) journal and digital object identifier (doi) (e) animal species, age, sex and strain, (f) type of stress (animal models), (g) durability of stress, (h) brain areas studied, (i) microglia markers, (j) neuroinflammatory markers, (k) neurogenic markers, (l) results, (m) behavioural effects, (n) treatments for reversing the effects of stress on

microglia, neurogenesis and depression-like behaviours and (o) relationships among the examined parameters. All studies were subjected to extraction in duplicate. During analysis of the literature, studies were discarded if they failed to meet the inclusion criteria.

3. Results

3.1. Earch results

Advanced searches yielded in 62 articles in PubMed, 70 articles in SCOPUS, 152 in Embase, 88 in the Web of Science and 28 in Medline. For Google Scholar, the first 200 references were collected (Bramer et al., 2017). Hence, 600 studies were initially identified. After removal of duplicates, 46 articles met the inclusion criteria for full-text review based on title and abstract information. Additional articles were identified by manual search of article reference lists. After a full text review for article eligibility, 17 articles were selected for qualitative analysis. All of the identified studies were evaluated (Fig. 1). In each section of results, the effects observed in animals stressed in early life or in adults have been described separately. Where this is not explicitly stated, it is because the studies reviewed have only assessed this parameter in animals stressed in adulthood.

3.2. Effect of psychosocial stress on depression-like behaviour in studies examining hippocampal microglia and neurogenesis

In the papers reviewed for this systematic review, the effect of stress on depressive-like behaviour has been assessed in animal models of depression that exhibit several depression symptoms, such as anhedonia, dysfunctional coping strategies, a deteriorated physical state, decreased energy or increased fatigue, maladjusted social interaction, cognitive impairment or psychomotor retardation (World Health Organization, 1992; American Psychiatric Association, 2013). (Table 1; Fig. 2).

3.2.1. Cognitive domains

Studies that assessed the effects of stress on cognitive domains used behavioural tests that rely on memory functions, particularly hippocampal-dependent memories. These alterations have been observed in both early developmental and adult periods. Maternal stress may have also had an impact on offspring, which may have developed short- and long-term health disorders and cognitive impairment. Thus, late maternal sleep deprivation induced spatial memory problems in prepuberty offspring, as measured by the Morris water maze (MWM) (Zhao et al., 2014).

In adult period, CUMS significantly impaired novel object recognition (Rimmerman et al., 2017). Chronic social defeat stress affected working memory, albeit moderately, and spatial memory recall, as evaluated by the Morris water maze and the Barnes test (McKim et al., 2016). Sleep deprivation also impaired spatial memory (Wadhwa et al., 2017).

3.2.2. Motor symptoms

Locomotor activity has been measured by the open field test (OFT), elevated plus maze (EPM), Morris water maze (MWM) and Barnes maze test, and it has been observed that stressed animals travel shorter distances in these mazes, possibly reflecting increased anxiety, impaired memory (Lee et al., 2019; McKim et al., 2016) or loss of motivation and

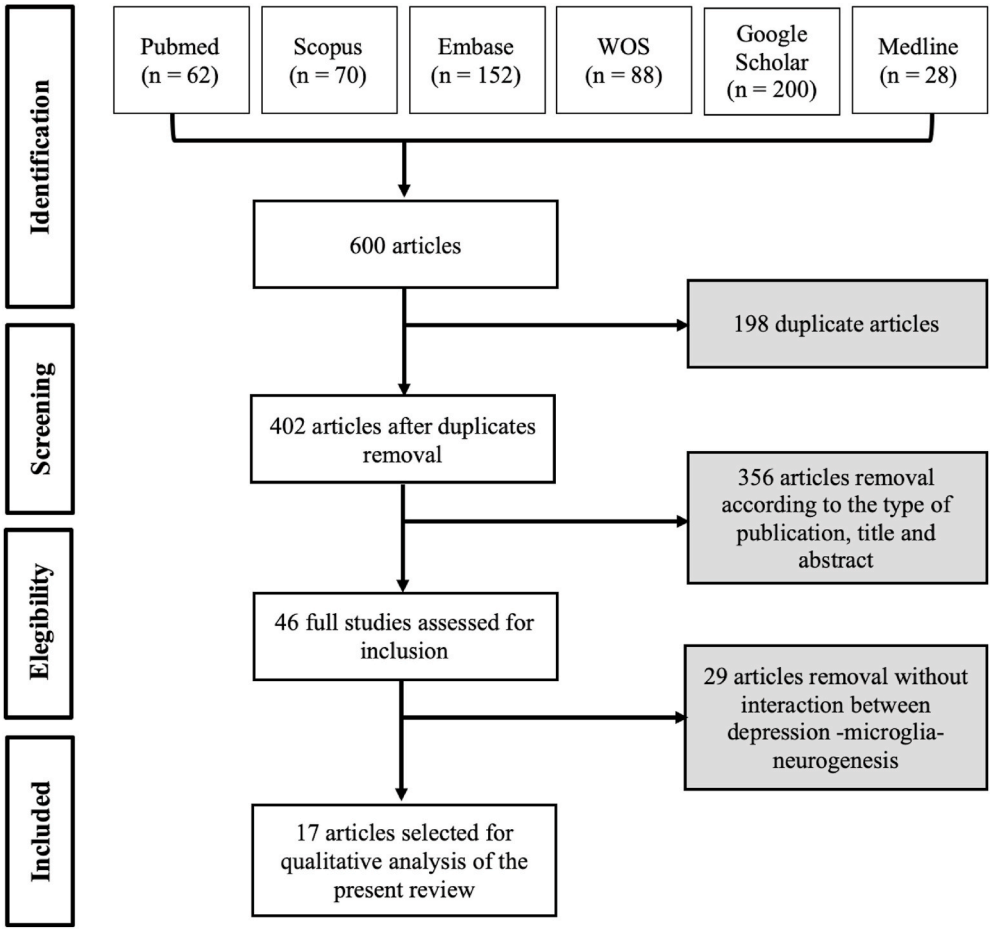

Fig. 1. Flow diagram for literature selection, following the PRISMA guidelines, for the development of the present systematic review.

Table 1
Effects of psychosocial stress on depression-like behaviours, microglia, inflammatory molecules and neurogenesis.

Stress Period	Stress	Test/Score	Behavioural Effects	Microglia	Pro-inflammation	Anti-inflammation	Proliferation	Differentiation	Study
Early-life stress	MS	FST SPT OFT	↑ Composite depression score (sucrose preference < mean of control and immobility time > mean of control). ↓ Time in the centre of open field.	↑% Activated microglia ↓ Branching microglia ↓ Relative mRNA level of CX3CR1	mRNA expression: ↑ IFN-γ ↑ IL-1β ↑ IL-6 ↑ iNOS ↑ TNF-α	mRNA expression: ↓ IL-4 ↓ TGF-β ↓ IL-1rα ↓ Ym-1 ↓ Arg-1	↓ BrdU+	↓ BrdU+/DCX+ (↑ with a 2nd Stress)	Han et al. (2019)
	Maternal SD	Body Weight MWM SPT	↓ Body weight. Later Maternal SD ↑ latency to find platform, the number of platforms crossing and the time in rewording quadrant of test day. Later Maternal SD altered spatial learning and memory of prepuberty offspring. ↓ Sucrose intake.	↑ Iba-1+ with large somas and short thick process and ameboid morphology (activated microglia) ↓ Iba-1+ with rod-shape with fine, ramified processes (resting microglia)	mRNA expression: PND1: ↑ IL1-β; ↑ IL-6; ↑ TNF-α PND7: ↑ IL-6; ↓ IL-1β PND14: ↑ IL-6; ↓ IL-1β PND21: ↑ IL-6; ↓ IL-1β	mRNA expression: ↓ IL-10	= BrdU+	↓ BrdU/DCX+	Zhao et al. (2014)
Adult stress	CUMS	FST SPT	↑ Immobility time. ↓ Sucrose intake.	↑ Number Iba-1+	mRNA expression and protein levels: ↑ IL-1β ↑ IL-6 ↑ TNF-α	–	–	↓ DCX+	Cheng et al. (2019)
	CUMS	Coat State Score Nest-Building Test	↓ State of the coat (↑ score). ↓ Nest-making behaviour.	↑ Density CD11 b/P2X7R+	–	–	–	= DCX+	Farooq et al. (2018)
	CUMS	FST OFT Social Exploration SPT	↓ (Slightly) latency of the first period of immobility. ↑ Immobility time (but without reaching significant differences). ↓ Distance moved in the centre of the OFT. ↓ Time in the centre of open field. ↓ Social exploration. ↓ Sucrose intake.	↓ Number (↑ in acute) ↓ Length processes ↓ Soma area (↑ in acute) ↓ CD11b mRNA ↓ CD200 mRNA	↓ IL-1β (acute) = IL-1β (chronic) ↑ IL-1 signalling	–	= BrdU+	–	Kreisel et al. (2014)
	CUMS	FST OFT TST	↑ Immobility time. ↓ Total distance. ↓ Time in the centre of the OF. ↑ Immobility time.	↑% Iba-1+ signal	Protein levels: ↑ IL-1β ↓ pro-IL-β ↑ TNF-α ↑ NLPR3 ↑ ASC	–	–	↓ DCX+	Lee et al. (2019)
	CUMS	Body Weight FST SPT TST	↓ Body weight. ↑ Immobility time. ↓ Sucrose intake. ↑ Immobility time.	↑ CD11b (MAC-1)	mRNA expression: ↑ IL-1β ↑ IL-6 ↑ TNF-α ↑ NLRP3	mRNA expression: ↓ IL-10	↓ BrdU+	↓ DCX+ ↓ β-tubulin III (Tuj-1)	Lu et al. (2014)
	CUMS	Object Recognition Test SPT	↓ In the novel object recognition memory. ↓ Sucrose intake.	↓ Iba-1+ (with reduced process)	–	–	–	↓ DCX+	Rimmerman et al. (2017)
	CUMS	Body Weight Coat State Score FST	= Body weight. ↓ State of the coat (↑ score). ↑ Immobility time.	↓ Iba-1+ ↑ Soma area (↓ thin and highly ramified	Peripheric/no central	Peripheric/no central	↓ BrdU+ ↓ Ki-67	↓ DCX+ ↓ Maturation of neurons	Vega-Rivera et al., 2020

(*continued on next page*)

Table 1 (*continued*)

Stress Period	Stress	Test/Score	Behavioural Effects	Microglia	Pro-inflammation	Anti-inflammation	Proliferation	Differentiation	Study
		SPT	↓ Sucrose intake.	processes; ↑ processes or = relative longer than soma) ↓ CX3CL1 ↓ CX3CR1					
	CUMS	Body Weight FST SPT TST	↓ Body weight. ↓ Latency ↑ Immobility time. ↓ Sucrose intake. ↓ Latency ↑ Immobility time.	↑ Iba-1+ (Ameboid: larger body and few shorter processes) ↑ CD11b (mRNA expression)	mRNA at 5 weeks: ↑ IL-1β ↑ IL-6 ↑ IFN- γ ↑ iNOS mRNA at 6 weeks: ↑ IL-1β ↑ IL-6 ↑ IFN- γ ↑ TNF-α mRNA at 7 weeks: ↑ IL-1β ↑ IL-6 ↑ iNOS Ratios: ↑ IL-1β/IL-1ra = iNOS/Arg-1 ↑ TNF-α/IL-10	mRNA at 5 weeks: ↓ Arg-1 ↓ TGF-β ↓ Ym-1 mRNA at 6 weeks: ↓ IL-4 ↓ TGF-β ↓ Ym-1 mRNA at 7 weeks: ↑ IL-10 ↓ IL-4 ↓ TGF-β ↓ Ym-1	= BrdU+	↓ BrdU/DCX+ ↓ (BrdU/DCX+)/ BrdU + ratio ↓ DCX+ ↓ DCX mRNA = Prolongations in DCX	Zhang et al. (2017)
	CUMS	FST NSFT SPT TST	↑ Immobility time. ↑ Latency to the first time feeding in the Novelty-suppressed feeding test. ↓ Sucrose intake. ↑ Immobility time.	↓ CD206+ ↓CD206+/Iba-1+	mRNA expression: ↑ iNOS ↑ TNF-α Protein levels: ↑ IL-1β ↑ IL-6 ↑ TNF-α	mRNA expression: ↓ Arg-1 Protein levels: ↓ IL-10	–	↓ DCX+ ↓ DCX protein levels	Zhong et al. (2019)
	CWIRS	Body Weight FST SPT TST	↓ Body weight. ↑ Immobility time. ↓ Sucrose intake. ↑ Immobility time.	↑ $CD68^{+}$	Protein levels: ↑ IL-1β ↑ TNF-α ↑ iNOS	–	–	↓ BrdU/DCX+	Mao et al. (2020)
	RSDS	Body Weight SIT	↑ Body weight. ↓ Time in social interaction zone when aggressor was introduced into the test.	↑ Iba-1+ ↓ CX3CR1+ ↑ NLRP3+	Protein levels: ↑ IL-6	–	↓ BrdU+ ↓ Ki-67+	↓ BrdU/DCX+	Ito et al. (2017)
	RSDS	FST SIT SPT TST	↑ Immobility time. ↓ Time in social interaction zone when aggressor was introduced into the test; and = time without aggressor. ↓ Sucrose intake. ↑ Immobility time.	↑ Iba-1+ (+activated microglia with larger cell bodies and thick-condensed processes)	mRNA expression: ↑ IL-1β ↑ IL-6 ↑ TNF-α (↑phosphorylation p65 NF-κB) ↑ iNOS ↑ COX	–	–	↓ DCX+	Jiang et al. (2020)
	RSDS	EPM OFT SIT	↑ Time in closed arm. ↓ Time in the centre of the OFT. ↓ Time in social interaction zone when aggressor was introduced into the test.	↑ Iba-1+	mRNA expression: ↑ IL-1β ↑ HMGB1 ↑ BIP ↑ XBP1 (ER stress)	mRNA expression: ↓ IL-10	–	↓ MAP-2	Liu et al. (2019)
	RSDS	Barnes Maze	Affected latency to find the escape hole. ↑ Number of errors. ↓ Spatial memory.	↑% Iba-1 area (with an increased soma and thickened processes) ↑ $CD45^{+}$	mRNA expression: ↑ IL-1β ↑ IL-6 ↑ TNF-α	–	= BrdU+	= DCX = mature at 0,5 d ↓ DCX/BrdU at 10 d	McKim et al. (2016)

(*continued on next page*)

Table 1 (*continued*)

Stress Period	Stress	Test/Score	Behavioural Effects	Microglia	Pro-inflammation	Anti-inflammation	Proliferation	Differentiation	Study
		MWM	↓ Spatial memory. ↓ Working memory.					↓ NeuN/BrdU + at 28 d = BrdU/GFAP + at 28 d	
		SIT	↓ Time in social interaction zone when aggressor was introduced into the test.						
	SD	Body Weight Food Intake	↓ Body weight. ↓ Food intake.	↑ Iba-1+ ↑ Soma density and area	mRNA expression and protein levels: ↑ IL-1β	mRNA expression and protein levels: ↓ IL-4	↓ BrdU+ ↓ Ki-67+	↓ DCX+ = NeuN+ ↓ BDNF+	Wadhwa et al. (2017)
		MWM	↑ Latency to find the platform. ↑ Path length to reach the platform. ↓ Path efficiency to reach the platform. ↓ Number of entries in the target zone. ↓ Time spent in the target zone. ↓ Spatial memory.	↓ Process and ramification (Suggesting activated microglia)	↑ IL-6 ↑ TNF-α	↓ IL-10			

Abbreviations. Arg-1: Arginase 1; ASC: apoptosis-associated Speck-like protein containing a CARD; BDNF: Brain-Derived Neurotrophic Factor; BIP: binding immunoglobulin protein; BrdU: Bromodeoxyuridine; CD(11 b, 45, 68, 200, 206): Cluster of Differentiation; CUMS: Chronic Unpredictable Mild Stress; CX3CL1: CX3C chemokine ligand 1; CX3CR1: CX3C chemokine receptor 1; CWIRS: Chronic Water Immersion Restraint Stress; DCX: Doublecortin; EPM: Elevated Plus Maze; ER: Endoplasmic Reticulum; FST: Forced Swimming Test; HMGB: High Mobility Group Box; Iba-1: Ionized calcium Binding Adapter molecule 1; IFN: Interferon; IL: Interleukin; iNOS: Inducible nitric oxide synthase; MAP-2: Mitogen-Activated Protein 2; MS: Maternal Separation; MWM: Morris Water Maze; NeuN: Neuronal Nuclei; NLPR3: Inflammasome; NSFT: Novelty-Suppressed Feeding Test; OFT: Open Field Test; P2X7R: P2X purinoceptor 7; PND: Post-Natal Day; RSDS: Repeated Social Defeat Stress; SD: Sleep Deprivation; SIT: Social Interaction Test; SPT: Sucrose Preference Test; TGF: Transforming Growth Factor; TNF: Tumor Necrosis Factor; TST: Tail Suspension Test; XBP1: X-Box Binding Protein 1; +: Positive cells.

energy (Harrington, 2012).

3.2.3. *Behavioural tests of loss of motivation, lack of energy and anhedonia*

Regarding behavioural tests for assessing depressive-like behaviour, the sucrose preference test has been widely used as a measure of anhedonia. Changes in body weight as a measure of changes in appetite, deterioration of state of the coat may be interpreted as the loss of interest in performing customary grooming and deficits in the ability of mice to make nests which indicates loss of energy or decreased motivation in major depression (Cryan and Holmes 2005; Deacon and Rawlins, 2006).

During early-life stress, maternal separation (MS) did not affect anhedonia but increased animals' vulnerability to secondary stressors (i.e., restraint). Thus, male pups subjected to maternal separation, unlike control pups, exhibited significant behavioural changes after exposure to a secondary stress during the adolescent period (Han et al., 2019). A loss of body weight was observed in offspring of mothers subjected to sleep deprivation (SD) (Zhao et al., 2014).

Consistently, in adults, chronic stress reduced the preference for sucrose, indicating anhedonia. Thus, CUMS (Cheng et al., 2019; Kim et al., 2016; Kreisel et al., 2014; Lu et al., 2014; Rimmerman et al., 2017; Vega-Rivera et al., 2020; Zhang et al., 2017; Zhong et al., 2019), chronic social defeat stress (Jiang et al., 2020) and chronic water immersion restraint stress (Mao et al., 2020) reduced sucrose intake. CUMS also induced deterioration of the coat (Farooq et al., 2018; Vega-Rivera et al., 2020) and resulted in deficits in the ability of mice to make nests (Farooq et al., 2018) and reduced body weight (Lu et al., 2014; Zhang et al., 2017). A reduction in body weight was also observed after chronic water immersion restraint stress (Mao et al., 2020), after chronic social defeat stress (Ito et al., 2017), in animals deprived of sleep (Wadhwa et al., 2017).

3.2.4. *Coping strategies tests*

In addition, several studies were designed to assess how stress influences coping strategies. Animals subjected to chronic stress tended to spend more time immobile than controls in classical tests that assess stress coping behaviour. In this regard, animals summited to CUMS (Cheng et al., 2019; Kreisel et al., 2014; Lee et al., 2019; Lu et al., 2014; Vega-Rivera et al., 2020; Zhang et al., 2017; Zhong et al., 2019) or chronic social defeat stress (Jiang et al., 2020) exhibited passive coping strategies in response to inescapable stressors in the FST, TST or both tests.

3.2.5. *Anxiety-like behavioural tests*

Comorbid anxiety and depression in clinical and epidemiologic samples is very common (Goodwin and Olfson, 2001). Several reports have confirmed the effect of psychological stress on anxiety, which often accompanies depression-like symptoms. Animals undergoing CUMS spent less time in the centre of the open field test (considered a test of anxiety) (Kreisel et al., 2014; Lee et al., 2019), made fewer crossings, travelled shorter distances in the central region (Lee et al., 2019) and exhibited increased latency to the first feeding in the novelty-suppressed feeding test (Zhong et al., 2019). Chronic social defeat stress also increased anxiety-like behaviour. Defeated mice spent less time in the centre zone in the open field test and more time in the closed arms of the elevated plus maze (Liu et al., 2019).

3.2.6. *Social interaction tests*

Positive social relationships have substantial benefits on mental health. Nevertheless, depressed individuals have more dysfunctional social relationships, resulting in less rewarding social interactions (Elmer and Stadtfeld, 2020) and avoidance of social contact (Masud et al., 2020). Both CUMS (Jiang et al., 2020; Kreisel et al., 2014) and chronic social defeat stress reduced social interaction (Ito et al., 2017; Liu et al., 2019; McKim et al., 2016), indicating that stressed animals exhibit social avoidance.

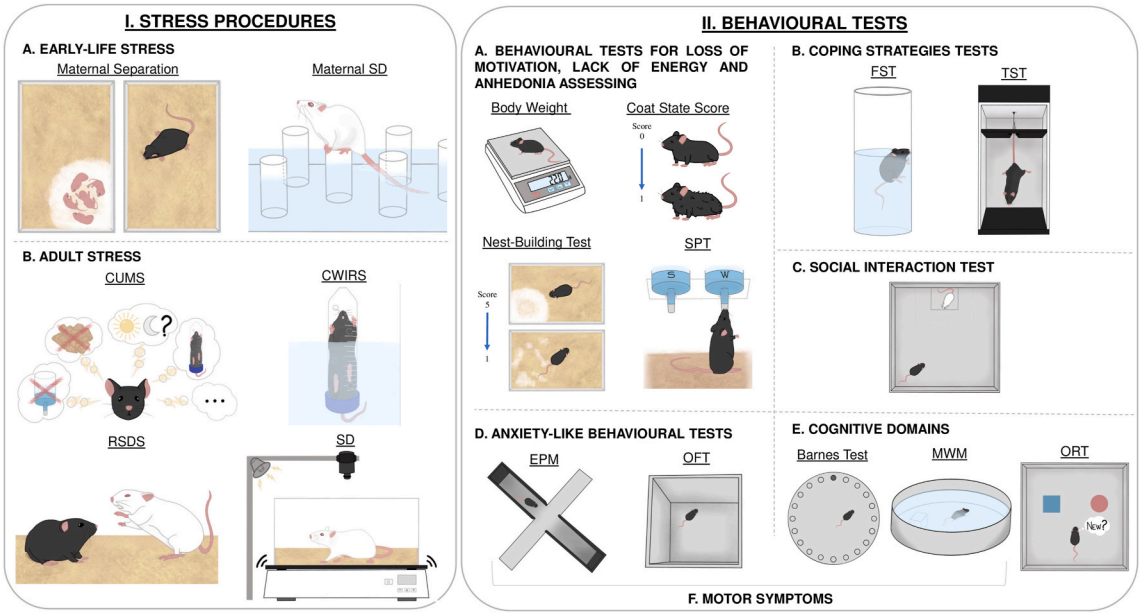

Fig. 2. I) Representation of the different stress procedures used in the 17 articles selected in this systematic review, and classified in early-life (A) or adult (B) stress. II) Different behavioural tests to measure the effect of psychosocial stress on depression-like behaviour. The tests are shown classified by the categories of: behavioural tests for loss of motivation, lack of energy and anhedonia assessing (A); coping strategies tests (B); social interaction test (C); anxiety-like behavioural tests (D); cognitive domains (E) and motor symptoms (F). Note that the last one category (motor symptoms) also uses EPM, OFT, Barnes Test and MWM. Also comment that, mice have been represented in behavioural tests as if they had depressive-like behaviours. Abbreviations. CUMS: Chronic Unpredictable Mild Stress; CWIRS: Chronic Water Immersion Restraint Stress; EPM: Elevated Plus Maze; FST: Forced Swimming Test; MWM: Morris Water Maze; OFT: Open Field Test; ORT: Object Recognition Test; RSDS: Repeated Social Defeat Stress; SD: Sleep Deprivation; SPT: Sucrose Preference Test; TST: Tail Suspension Test.

3.3. *Effect of psychosocial stress on hippocampal neurogenesis*

Adult neurogenesis is a process that takes place in multiple steps, including proliferation, differentiation, migration, and synaptic integration of post-mitotic newly functional cells. The expression of several markers correlates with several phases of neurogenesis (von Bohlen und Halbach, 2007). Markers that were widely used in the research included in this review to investigate the impact of stress on adult hippocampal neurogenesis were Ki67, a marker used to identify proliferating cells; BrdU (5-bromo-2′-deoxyuridine), which labels proliferating neural progenitor cells (NPCs) in the dentate gyrus (DG) and may be used to identify proliferation or survival of new cells depending on the time between its administration and sacrifice; and doublecortin (DCX), which is a marker of the maturation of new neurons. Moreover, the ratio of BrdU+/DCX + cells to BrdU + cells was used to assess the levels of neuronal differentiation of new-born cells in the hippocampus (Han et al., 2019). Furthermore, other markers have also been used, such as β-tubulin III, (a neuronal marker), microtubule-associated protein 2 (MAP-2), (a marker of neuronal differentiation), the astrocytic marker glial fibrillary acidic protein (GFAP) and neuronal nuclear protein (NeuN), (a useful marker of mature neurons). The following discussion is an indication of how psychological stress affects the different phases of neurogenesis (Table 1).

3.3.1. *Effects of psychosocial stress on the proliferation of neural progenitor cells*

3.3.1.1. Early-life stress. The effect of sleep deprivation on hippocampal proliferation was observed in offspring of mothers subjected to sleep deprivation. In this sense, middle and later maternal sleep deprivation affected the number of BrdU + cells in the DG of offspring (Zhao et al., 2014). Maternal separation followed by a second stressor led to noticeably fewer proliferative cells, as determined by BrdU staining (Han et al., 2019).

3.3.1.2. Adult stress. CUMS decreased the total number of Ki-67+ cells (Vega-Rivera et al., 2020) and the generation of BrdU-labelled DG cells (Lu et al., 2014). Similarly, chronic social defeat stress reduced the expression of Ki-67 in the DG (Ito et al., 2017).

Sleep deprivation reduced the number of Ki-67+ and BrdU + cells, suggesting a reduction in proliferation (Wadhwa et al., 2017). In contrast, chronic social defeat stress did not induce changes in the number of BrdU + cells, as determined 12 h after the completion of the chronic social defeat stress protocol (McKim et al., 2016).

3.3.2. *Survival*

According to the time between BrdU administration and sacrifice, the survival of the new-born cells may be studied. CUMS (Vega-Rivera et al., 2020) and chronic social defeat stress (Ito et al., 2017) reduced cells survival, as assessed by BrdU administered at least 4 days before perfusion of animals (Mandyam et al., 2007).

3.3.3. *Differentiation*

3.3.3.1. Early-life stress. Maternal separation followed by a second stressor reduced the ratio of BrdU+/DCX + cells to BrdU + cells, which was used to assess the degree of differentiation of new-born cells in the hippocampus (Han et al., 2019). Similarly, a decreased ratio of BrdU + DCX+/BrdU + cells was observed in the offspring of mothers subjected to middle and late sleep deprivation (Zhao et al., 2014).

3.3.3.2. Adult stress. CUMS decreased the total number of DCX + cells (Cheng et al., 2019; Lu et al., 2014; Rimmerman et al., 2017; Vega-Rivera et al., 2020; Zang et al., 2017; Zhong et al., 2019), which is considered indicative of the number of neural progenitor cells (Zhong et al., 2019). Moreover, CUMS reduced the expression of β-tubulin III in the GCL and hilar SGZ margin (Lu et al., 2014). However, no significant differences were observed between the control and stressed groups with respect to the density of DCX (Farooq et al., 2018). Conversely, the number of DCX+/BrdU + cells in the SGZ of the hippocampus decreased

markedly in the CUMS group compared to control animals (Farooq et al., 2018).

On the other hand, the opposite effects were observed regarding the degree of maturation of new-born neurons after CUMS. The absolute number of more immature cells (lacking protrusions) was increased in the stressed group compared to the control group. In contrast, stress reduced the absolute number of more mature cells (those with dendrites longer than the soma and at least one node with dendrites in the granular cell layer (GCL) or cells with a mature appearance showing at two branching points and dendrites reaching the molecular layer (ML) (Vega-Rivera et al., 2020).

Chronic social defeat stress exposure reduced the numbers of BrdU+/DCX + cells (Ito et al., 2017) and MAP-2+ cells in the hippocampus (Liu et al., 2019). Regarding the number of DCX + cells, compared to control treatment, chronic social defeat stress did not induce changes in the number or proportion of mature or immature cells (McKim et al., 2016). These results indicate that the total number of young neurons in the DG of the hippocampus was unaffected by chronic social defeat stress after 12 h. However, the fate of NPCs may be affected by chronic social defeat stress over time (McKim et al., 2016). In fact, chronic social defeat stress significantly reduced the proportion of DCX+/BrdU + cells 10 days after injection of BrdU (McKim et al., 2016), as well as the number of DCX + cells four (Ito et al., 2017) or six days (Jiang et al., 2020) after completion of the chronic social defeat stress protocol. Similarly, the total number of BrdU + cells expressing the mature neuronal marker NeuN was reduced in animals 28 days after completion of the chronic social defeat stress protocol. No differences were observed in the number of BrdU+/GFAP+ (used as marker of astrocytes) cells 28 days after completion of the stress protocol (McKim et al., 2016). Another stressor, chronic water immersion restraint stress, significantly reduced the number of BrdU+/DCX + cells in the DG area of the hippocampus (Mao et al., 2020).

3.4. Effects of psychosocial stress on microglia and inflammatory molecules

Immunohistochemical markers are commonly used to study changes in microglia after stress. A high degree of plasticity and diversified morphology are relevant characteristics of microglia (Zhang et al., 2018). With some exceptions, microglial morphology and function tend to be closely related (Boche et al., 2013; Fernández-Arjona et al., 2017, 2019; Nayak et al., 2014). Therefore, analysis of microglial morphology may be a useful approach to determine the effects of psychological stress on microglial status, which may be involved in the pathogenesis of depression (Zhang et al., 2018). A broad range of microglial markers allows the study of changes in microglial number and morphology (Table 1).

3.4.1. 1- Ionized calcium-binding adapter molecule-1 (Iba-1)

Among all markers, the most widely employed is ionized calcium-binding adaptor protein-1 (Iba-1), a 17-kDa actin-binding protein that is specifically and constitutively expressed in microglia (Imai et al., 1996; Ahmed et al., 2007). In fact, the majority of research articles included in the review examined the effect of stress on microglial number or morphology using Iba-1.

3.5. Early-life stress

Maternal separation induced a slight increase in the number of activated microglia. This effect was even more pronounced in maternally separated mice exposed to a second stressor, which exhibited an increased proportion of activated microglia characterized by fewer branches and shortened processes compared to control animals (Han et al., 2019). Microglia in the offspring of sleep deprivation mothers also showed an increase in activation status. Maternal sleep deprivation promoted an increase in the number of microglia and changes in microglial morphology marked by a reduction in microglia with rod-shaped cell bodies and fine, ramified processes and an increase in microglia with small cell bodies and long thin processes or with large somas, short thick processes, and a rounded ameboid morphology in offspring (Zhao et al., 2014).

3.6. Adult stress

While it is traditionally believed that stress induces an increase in microglial number, which may be involved in depression, some studies did not find increased microglial numbers after stress and even observed that a decrease in microglia may be connected to depression induced by stress (Yirmiya et al., 2015). In fact, both effects have been observed after exposure to the same stressor. CUMS was shown to cause either intense activation of microglia or a decrease in and suppression of microglial function in specific brain areas (Table 2). An increase in the number of Iba-1+ cells (Cheng et al., 2019; Lee et al., 2019; Zhang et al., 2017) with an ameboid shape, which represents a broad range of morphological changes, including thicker and shorter processes, a larger cell body, and fewer branches, in the hippocampus was observed (Zhang et al., 2017). The opposite phenomenon has also been reported. CUMS also induced a decreased number of microglia with an increased soma area (Vega-Ribera et al., 2020) or even a reduced number of microglia, with some adopting a dystrophic morphology reflected by overall significant reductions in the length of microglial processes (Kreisel et al., 2014; Rimmerman et al., 2017) and the soma area (Kreisel et al., 2014). Interestingly, this same treatment in the acute phase resulted in an increase in the number of Iba-1+ cells with an increased soma area (Kreisel et al., 2014).

On the other hand, the effects of chronic social defeat stress on microglial number and morphology were more homogeneous, involving an increase in the number of microglia (Ito et al., 2017; Jiang et al., 2020; Liu et al., 2019; McKim et al., 2016). In that case, microglia were characterized by larger cell bodies with thick and condensed processes (Jiang et al., 2020; McKim et al., 2016). After chronic water immersion restraint stress, an increase in the intensity of microglial markers was observed, which was reinforced by an increase in the protein level of Iba-1 (Mao et al., 2020).

Immunoreactivity of Iba-1 in the DG, CA1 and CA3 regions of the hippocampus was increased in animals that were sleep deprived for 48 h. Moreover, 48 h of sleep deprivation significantly altered microglial morphology, increased soma density and area and decreased sum inters, mean inters ramification index and microglial length (Wadhwa et al., 2017).

3.6.1. Other markers of microglial status: CD11b, P2X7R, CD200; CD206, CD68; activation of protein kinases

Iba-1 labelling is not the only approach used to study changes in microglial morphology induced by stress. Other markers, such as *cluster of differentiation molecule 11b* (CD11b, also known as macrophage-1 Ag, MAC-1), which is also expressed by microglia, are commonly used. In the DG of the hippocampus, CUMS caused increased expression of CD11b in the microglia of the DG, indicating overactivation of microglia in this region (Lu et al., 2014). Moreover, activation and increases in microglia expressing P2X7 receptors, which acts via ATP, the second signal to the inflammasome activation, which induces both maturation and release of proinflammatory cytokines, such as IL-1β and IL-18, have also been observed (Farooq et al., 2018). mRNA expression levels of CD11b quantified by RT-PCR has also been used as an indicator of microglial activation status and were either elevated (Zhang et al., 2017) or reduced (Kreisel et al., 2014) in animals subjected to CUMS.

The expression of the neuronal marker CD200, which normally maintains microglia in relative quiescence, was also reduced after exposure to CUMS (Kreisel et al., 2014), and the ratio of CD206+ cells (a manose receptor regarded as an anti-inflammatory biomarker, which is involved in tissue recovery and function restoration (Perego et al.,

2011)) to Iba-1+ mRNA was decreased following CUMS exposure (Zhong et al., 2019), suggesting that stress induced the activation microglia.

CD68 is a common marker of macrophage lineage cells and is primarily localized in more activated microglia within the brain parenchyma; although there is some CD68 expression on resting microglia (Lee et al., 2002), CD68 labels the lysosome and is therefore commonly considered a marker of activated phagocytic microglia. Evaluation of activated microglia by CD68 immunostaining showed a significant elevation of $CD68^{+}$ cells in the DG area of animals subjected to chronic water immersion restraint stress (Mao et al., 2020) (Table 1).

3.6.2. The fractalkine (or CX3CL1) signalling pathway

Microglial cells interact with neurons and synapses through several chemokine signalling pathways. The fractalkine (or CX3CL1) signalling pathway is one of the most important pathways (reviewed in Arnoux and Audinat, 2015) that interacts with microglia through the CX3CR1 receptor (Vega-Rivera et al., 2020) and is involved in decreasing microglial activation.

This signalling pathway also tended to be less activated in mice subjected to early-life stress (i.e.) maternally separated mice than in control mice (Han et al., 2019).

CUMS, in adult period, decreased the immunoreactivity of CX3CL1 (fractalkine) and CX3CR1 in the dentate gyrus (Vega-Rivera et al., 2020).

3.6.3. Expression of proinflammatory and anti-inflammatory markers induced by psychosocial stress

The main source of proinflammatory and immune regulatory cytokines in the brain is microglia (Kreisel et al., 2014; Lehmann et al., 2018), which may induce a toxic environment in the brain under certain conditions (Felger et al., 2013; Lehmann et al., 2018). Increased microglial activation results in the production of proinflammatory cytokines. The cascade of inflammatory events induced by stress may be orchestrated by several factors. The studies examined for this review took into account some aspect of the neuroinflammatory hierarchical cascade initiated by microglial activation. Some studies focused on the initial steps of the neuroinflammatory cascade, and some of them examined end products of the inflammatory cascade that may suggest the activation induced by stress of the whole cascade of neuroinflammatory events (Table 1).

Table 2
Effects of chronic unpredictable mild stress (CUMS) on the microglia number and morphology (Iba-1 positive cells).

Duration	Strain	Aged	Number	Morphology	Study
3 weeks	BALB/c mice	24 weeks old	↑	Ameboid: Larger body and few shorter processes.	Lee et al. (2019)
5 weeks	C57BLJ	8–16 weeks old	↓	Atrophic: reduction length processes and area.	Kreisel et al. (2014)
5 weeks	C57BLJ	3–4months old	↓	In DG not in CA3; length processes reduced.	Rimmerman et al. (2017)
7 weeks	BALB/c mice	8 weeks old	↓	Increase of some area.	Vega-Rivera et al., 2020
7 weeks	C57BLJ	7–8 weeks old	↑	Ameboid: Larger body and few shorter processes.	Zhang et al. (2017)
8 weeks	C57BL/6	8 weeks old	↑	–	Cheng et al. (2019)

Abbreviations. DG: Dentate Gyrus; CA3: Cornu Ammonis 3.

In this sense, concerning the first steps of the cascade, high expression of cytoplasmic HMGB1 (high mobility group box 1 protein) has been observed in mice exposed to chronic social defeat stress (Liu et al., 2019). Western blotting results clearly suggested that chronic water immersion restraint stress (Mao et al., 2020) and chronic social defeat stress (Jiang et al., 2020) significantly increased the phosphorylation of p65, one of the five components of NF-κB and hence may activate NF-κB. Additionally, chronic social defeat stress decrease SIRT1 expression and in turn increased the levels of acetylated p65 in the hippocampus (Jian et al., 2020).

Cytokine-related findings were consistent across studies in relation to the production of IL-1β. Most studies found that psychological stress increased the central levels of IL-1β.

In early-life stressed animals, an increase in IL-1β levels was observed both after maternal separation (Han et al., 2019) or in offspring of sleep-deprived mothers, in PND1, PND7 and PND14. In contrast, a reduction of this cytokine was observed in PND21 (Zhao et al., 2014).

An increase in IL-1β has also been observed in stressed animals in adulthood. Thus, mice exposed to CUMS (Cheng et al., 2019; Lee et al., 2019; Lu et al., 2014; Zhang et al., 2017; Zhong et al., 2019), chronic social defeat stress (Jiang et al., 2020; Liu et al., 2019; McKim et al., 2016), chronic water immersion restraint stress (Mao et al., 2020), and sleep deprivation (Wadhwa et al., 2017).

Given that IL-1β is one the first cytokines involved in the hierarchical cytokine signalling cascade in the central nervous system (Basu et al., 2004) the results of most of the studies reviewed here, indicated that psychological stress, irrespective of stress condition, increased neuroinflammation. Conclusive evidence for the effect of maternal exposure to sleep deprivation on offspring or the effect of prolonged CUMS requires further research on inflammatory cytokines.

The levels of IL-6 were also increased after exposure maternal separation (Han et al., 2019) in offspring of sleep deprivation mothers (Zhao et al., 2014). TNF-α expression also increased after exposure to maternal separation (Han et al., 2019) or on PND1 in the offspring of mothers exposed to sleep deprivation (Zhao et al., 2014).

Increased levels of IL-6 were also observed in stressed animals in the adult period. Thus, an increase of this cytokine was observed after exposure to CUMS (Cheng et al., 2019; Zhang et al., 2017; Zhong et al., 2019), to chronic social defeat stress (McKim et al., 2016), and to sleep deprivation (Wadhwa et al., 2017). Similarly, TNF-α expression increased after exposure to CUMS (Cheng et al., 2019; Zhang et al., 2017; Zhong et al., 2019), chronic social defeat stress (McKim et al., 2016), chronic water immersion restraint stress (Mao et al., 2020), or sleep deprivation (Wadhwa et al., 2017).

The levels of IFN-γ were examined in only two studies, one of them used a stress protocol applied in the sensitive period of development and the other in the adult period. The results of which revealed that both maternal separation followed by a second stress (Han et al., 2019) and CUMS induced an increase in the levels of this cytokine (Zhao et al., 2014). On the other hand, inducible oxide synthase (iNOS) was highly expressed upon activation of the transcription factor nuclear factor-kappa B (NF-κB) in response to many stimuli, including IL-6, TNF-α and IFN-γ (Hibbs et al., 1988; Xie et al., 1994). Although the effect of psychosocial stress on the upregulation of inducible oxide synthase (iNOS) expression was examined in only four studies, an increase in the level of this enzyme was observed after maternal separation followed by a second stressor (Han et al., 2019), CUMS (Zhang et al., 2017) and chronic water immersion restraint stress (Mao et al., 2020). Interestingly, the levels of some proinflammatory cytokines that are involved in the upregulation of inducible oxide synthase (iNOS) expression were also increased after exposure to maternal separation (Hand et al., 2019), CUMS (Zhang et al., 2017), and chronic water immersion restraint stress (Mao et al., 2020).

The data on anti-inflammatory cytokines and chemokines are less consistent. For instance, the levels of anti-inflammatory cytokines, such

as IL-10, decreased after exposure to CUMS (Lu et al., 2014; Zhong et al., 2019), maternal exposure to sleep deprivation (Zhao et al., 2014) and exposure to sleep deprivation (Wadhwa et al., 2017) but increased 6 and 7 weeks after exposure to CUMS (Zhang et al., 2017) or remained unchanged after exposure to chronic social defeat stress (Liu et al., 2019). Similarly, Arg-1 mRNA levels decreased after exposure to maternal separation and 5 weeks after exposure to CUMS (Han et al., 2019; Zhang et al., 2017) but increased 6 weeks after exposure to CUMS. Significantly lower concentrations of the anti-inflammatory cytokines IL-4 (Han et al., 2019; Wadhwa et al., 2017; Zhang et al., 2017), TGF-β, Ym-1 and IL-1rα (Han et al., 2019) were also observed in response to psychological stress applied in both early-life (Han et al., 2019) and adult periods (Wadhwa et al., 2017; Zhang et al., 2017).

Overall, although not consistent, an imbalance in inflammatory homeostasis has been observed with an increase in the levels of proinflammatory molecules and a decrease in the levels of anti-inflammatory molecules. These effects were independent of the period of life in which the stressor was applied.

An increase in the levels of proinflammatory cytokines has primarily been observed after chronic stress but this is not the only change that has been found. Twenty-four hours after exposure to uncontrollable stress for two days, expression of IL-1ra was decreased, and expression of IL-1 receptor type I (IL-1R) was increased in animals, suggesting an increase in IL-1 signalling (Kreisel et al., 2014).

3.7. Association between microglial changes and neurogenesis impairments

Several studies have indicated that stress-induced changes in microglia that contribute to reductions in neurogenesis and neuronal plasticity are important contributors to the etiopathogenesis of depression (Cohen et al., 2016; Gemma et al., 2010; Kreisel et al., 2014; Sierra et al., 2010, 2014; Valero et al., 2016; Yirmiya et al., 2015). Nevertheless, only 6 studies examined the effects of treatments that directly target changes in microglial activation induced by stress on the neurogenic response (Farooq et al., 2018; Han et al., 2019; Kreisel et al., 2014; Liu et al., 2019; McKim et al., 2016; Wadhwa et al., 2017).

The rest of the studies that examined the effect of microglial impairment on the suppression of neurogenesis used a more indirect approach, such as antidepressant treatments, which reduced microglial impairment and simultaneously induced improvements in neurogenesis (Table 3).

3.7.1. Treatments that inhibit microglial changes induced by stress

Administration of minocycline, an antibiotic commonly used to inhibit microglial activation, in animals submitted to early-life stress, ameliorated the expression of proinflammatory cytokines in the hippocampus and mitigated hippocampal neurogenesis deficits induced by maternal separation followed by a second stressor. Thus, minocycline reversed the significant increases in the levels of the proinflammatory cytokines IL-1β and IL-6 and the significant decreases in the levels of the anti-inflammatory cytokines TFG-β and IL-4 and mitigated the increase in the IL-6+ Iba-1+/Iba-1+ ratio and Arg-1+ Iba-1+/Iba-1+ ratio induced by two exposures to maternal separation followed by a second stressor. These anti-inflammatory changes in response to minocycline treatment were associated with neurogenic changes depending on the stage of adult neurogenesis, suggesting that responses to minocycline are influenced by the steps of the neurogenic process. Thus, minocycline did not reverse the marked reduction in the number of proliferative cells induced by maternal separation but increased the level of differentiation after the second stressor. Minocycline led to significant upregulation of DCX expression in the hippocampus and BDNF expression following a second stressor (Han et al., 2019).

In adulthood, administration of minocycline did not prevent long-term deficits in response to chronic social defeat stress in proliferating neural progenitor cells, as similar reductions in the percentage of BrdU + cells that were NeuN+ were observed in minocycline-treated animals and vehicle-treated animals (McKim et al., 2016). However, minocycline blocked the reduction in Ki-67 and BrdU expression induced by sleep deprivation. Similarly, no changes in the number of DCX + cells were observed in minocycline-treated animals exposed to sleep deprivation compared to control animals during the stress protocol. The number of DCX + cells tended to remain at basal levels, suggesting that the inflammatory response induced by an increase in microglial activity may be involved in neurogenesis impairment induced by sleep deprivation (Wadhwa et al., 2017).

The P2X7 receptor (P2X7R) is a member of the purinergic receptor family that plays a pivotal role in stress-induced inflammation (Koo and Duman, 2008, 2009a, 2009b) and may be involved in the modulation of essential mechanisms of stress responses, such as neurogenesis (Csölle et al., 2013). A P2X7 receptor antagonist (Brilliant blue G, BBG) may be a valuable tool for determining the effect of a reduction in the activation of microglia induced by stress on hippocampal neurogenesis. However, while this antagonist reversed the activation of microglia expressing P2X7 receptors, reducing the increase in the density of CD11 b/P2X7R + cells in the molecular layer of the dentate gyrus (Farooq et al., 2018), it did not have any effect on the number of DCX+ in mice exposed to CUMS (Farooq et al., 2018).

Pre-treatment with recombinant human high-mobility group box 1-mediated microglial activation (HMGB1) protein receptor (rHMGB1) reduced microglial number, decreased the expression of neuroinflammatory markers, increased expression of HMGB1 and decreased the levels of indicators of endoplasmic reticulum damage (BIP and XBP1) but did not cause changes in MAP-2 expression (Liu et al., 2019). Probably this effect may be mediated by a translocation into nucleus of HMGB1 and a reduction of its transcription induced by rHMGB1 (Liu et al., 2019; Todorovaand and Evdokia, 2015).

Currently, the most commonly used approach to induce inflammation is administration of lipopolysaccharide (LPS), a bacterial endotoxin. LPS increased the number of microglia in the DG, which was reduced after 7 weeks of exposure to CUMS. In addition to normalizing microglial number, which was reduced by CUMS, LPS provoked a strong increase in the number of BrdU + cells, reversing the CUMS-induced suppression of microglial proliferation and atrophy (Kreisel et al., 2014).

3.7.2. Treatments with antidepressant properties

In addition to minocycline, BBG, rHMGB1 or LPS, other treatments with indirect mechanisms and antidepressant properties have also been used to study the relationship between microglial changes and neurogenic impairments. These compounds include antidepressant drugs, hormones such as melatonin, a phosphodiesterase 4 inhibitor and traditional oriental medicine formulations with antidepressant properties.

3.7.2.1. Antidepressant drugs. Fluoxetine, a highly selective serotonin reuptake inhibitor, rescued the decreased expression of HMGB1 and p65 induced by chronic social defeat stress. Surprisingly, although it had a slight effect on the increase in Iba-1 expression induced by stress, fluoxetine increased TNF-α and IL-1β mRNA expression in animals exposed to chronic social defeat stress. Animals subjected to social defeat stress also exhibited an increased number of receptors to which HMGB1 binds, such as advanced glycation end products (RAGE) and TLR4 receptors. Fluoxetine did not prevent increases in RAGE levels but attenuated the increase in TLR4 expression induced by chronic social defeat stress. In parallel, this antidepressant had a weak effect on the decrease in the expression of MAP-2 induced by chronic social defeat stress (Liu et al., 2019). Moreover, fluoxetine reversed the changes in microglial expression of P2X7 receptors caused by CUMS and, in a parallel manner, increased the number of DCX + cells (Farooq et al., 2018).

Citalopram, an antidepressant that selectively inhibits serotonin

Table 3
Association between microglial changes and neurogenesis impairments.

Treatment	Microglia[a]	Pro-inflammation[a]	Anti-inflammation[a]	Proliferation[a]	Differentiation[a]	Depression[a]	Study
BBG	↓ Density CD11 b/P2X7R+	–	–	–	= DCX+	↑ State of coat ↑ Nest building	Farooq et al. (2018)
Caffeine	↓ $CD68^{+}$ ↓ Protein of CD68 and Iba-1	Protein levels: ↓ IL-1β ↓ TNF-α ↓ iNOS	–	–	↑ BrdU/DCX+	↑ Sucrose intake ↓ Immobility in FST and TST	Mao et al. (2020)
Citalopram	↑ Iba-1+ = Soma area (↑ thin and highly ramified processes) ↑ CX3CL1 ↑ CX3CR1	–	–	–	–	= Body weight = State of coat ↑ Sucrose intake ↓ Immobility in FST	Vega-Rivera et al., 2020
$CX3CR1^{-/-}$ mice	= Iba-1+ = Reduced process (reduced by stress)	–	–	–	↓ DCX+ (basal not after stress)	↑ Sucrose intake ↑ Object recognition (5 weeks and 2 days)	Rimmerman et al. (2017)
Escitalopram	= CD206/Iba-1+	mRNA expression: ↓ iNOS ↓ TNF-α Protein levels: ↓ IL-1β ↓ IL-6	mRNA expression: = Arg-1 = CD206	–	↑ DCX+ ↑ DCX protein levels	↓ Immobility in FST and TST ↑ SPR in SPT = Crossing and rearing in OFT	Zhong et al. (2019)
FCPR16	↑ CD206/Iba-1+	mRNA expression: ↓ iNOS ↓ TNF-α Protein levels: ↓ IL-1β ↓ IL-6 ↓ TNF-α	mRNA expression: ↑ Arg-1 ↑ CD206 Protein levels: ↑ IL-10	–	↑ DCX+ ↑ DCX protein levels	↓ Immobility in FST and TST ↑ SPR in SPT = Crossing and rearing in OFT	Zhong et al. (2019)
Fluoxetine	↓ Density CD11 b/P2X7R+	–	–	–	↑ DCX+	↑ State of coat ↑ Nest building	Farooq et al. (2018)
Fluoxetine	= Iba-1+	mRNA expression: ↓ IL-1 β ↓ HMBG1	–	–	= MAP-2	= Social behaviour in SIT = Time in centre or open arm (OFT; EPM)	Liu et al. (2019)
Fluoxetine	↓ MAC-1 (CD-1)	–	–	↑ BrdU+	↑ DCX+ ↑ β-tubulin III (Tuj-1)	↑ Body weigh ↑ Sucrose intake ↓ Physical degradation ↓ Immobility in FST and TST	Lu et al. (2014)
Fluoxetine	↓ $CD68^{+}$ ↓ Protein of CD68 and Iba-1	Protein levels: ↓ IL-1β ↓ TNF-α ↓ iNOS	–	–	↑ BrdU/DCX+	↑ Sucrose intake ↓ Immobility in FST and TST	Mao et al. (2020)
Icariin	↓ Iba-1+	mRNA expression: ↓ IL-1 β ↑HMBG1citoplasm ↓ HMBG1 nuclear ↑ p65 ↓ BIP ↓ XBP1 (ER stress) ↑ Iκβ	–	–	↑ MAP-2	= Social behaviour in SIT ↑ Time in centre or open arm (OFT; EPM)	Liu et al. (2019)
Icaritin	↓ Iba-1+	mRNA expression: ↓ IL-1β ↑ HMBG1 ↓ BIP	mRNA expression: ↑ IL-10	–	↑ MAP-2	= Social behaviour in SIT = Time in centre, ↑ open arm (OFT; EPM)	Liu et al. (2019)

(*continued on next page*)

Table 3 (*continued*)

Treatment	Microglia[a]	Pro-inflammation[a]	Anti-inflammation[a]	Proliferation[a]	Differentiation[a]	Depression[a]	Study
		↓ XBP1 (ER stress) ↑ Iκβ					
Imipramine	↓ Iba-1+	mRNA expression: ↓ IL-1β ↓ IL-6 ↓ TNF-α (↓ Acetylation p65) Regulated MAPK pathway.	–	–	↑ DCX+	↑ Social interaction ↓ Immobility in FST and TST	Jiang et al. (2020)
Imipramine	Blocked decline	–		–	–	↓ Immobility in FST	Kreisel et al. (2014)
Iptakalin	↓ MAC-1 (CD-1)	mRNA expression: ↓ IL-1β ↓ IL-6 ↓ TNF-α ↓ NLRP3 Inhibit translocation to nuclear of p65	mRNA expression: ↑ IL-10	↑ BrdU+	↑ DCX+ ↑ β-tubulin III (Tuj-1)	↑ Body weigh ↑ Sucrose intake ↓ Physical degradation ↓ Immobility in FST and TST	Lu et al. (2014)
Kososan	↓ Iba-1+ (+aggregates) ↑ CX3CR1+ ↓ NLRP3+	Protein levels: ↓ IL-6	–	↑ BrdU+ = Ki-67+	↑ DCX+	↑ Social interaction	Ito et al. (2017)
LPS	↑ Iba-1+	–		↑ BrdU+	–	–	Kreisel et al. (2014)
Melatonin	↑ Iba-1+ ↓ Soma area (↑ thin and highly ramified processes) ↑ CX3CL1 ↑ CX3CR1	–	–	↑ BrdU+ ↑ Ki-67	↑ DCX+ ↑ Maturation of neurons	= Body weight ↑ State of coat ↑ Sucrose intake ↓ Immobility in FST	Vega-Ribera et al. (2020)
Minocycline	↓% Activated microglia ↑ Branching microglia ↑ Relative mRNA level of CX3CR1	mRNA expression: ↓ IFN-γ ↓ IL-1β ↓ IL-6 ↓ iNOS ↓ TNF-α ↓ (IL-6/Iba-1+)/Iba-1+	mRNA expression: ↑ IL-4 ↑ TGF-β ↑ IL-1rα ↑ Ym-1 ↑ Arg-1 ↑(Arg-1/Iba-1+)/Iba-1+	= BrdU+	↑ BrdU/DCX+ (attenuated ↓BDNF)	↑ Sucrose intake ↓ Composite depression score ↑ Time in centre of OFT	Han et al. (2019)
Minocycline	Blocked decline	–	–	–	–	↑ Sucrose intake ↑ Social exploration	Kreisel et al. (2014)
Minocycline	↓% Iba-1 area ↓ $CD45^{+}$	mRNA expression: ↓ IL-1β	–	–	= NeuN/BrdU+	↓ Latency and error in Barnes = Social preference in SIT	McKim et al. (2016)
Minocycline	↓ Iba-1+ ↓ Soma density and area ↑ Process and ramification (Suggesting ↓activated microglia)	mRNA expression and protein levels: ↓ IL-1β ↓ IL-6 ↓ TNF-α	mRNA expression and protein levels: ↑ IL-4 ↑ IL-10	↑ BrdU+ ↑ Ki-67+	↑ DCX+ ↑ BDNF+	In MWM: ↓ Latency to find the platform ↓ Path length to reach the platform ↑ Efficacy	Wadhwa et al. (2017)
Myelophil	↓% Iba-1+ signal	Protein levels: ↓ IL-1β ↓ TNF-α ↓ NLPR3 (↓ ASC, pro-IL-1β; mature IL-1β)	–	–	↑ DCX+	↓ Anxiety in OFT ↓ Immobility in FST and TST	Lee et al. (2019)
n-acetyl-cysteine (NAC)	↓% Iba-1+ signal	Protein levels: ↓ TNF-α ↓ IL-1β ↓ ASC	–	–	–	↑ Distance in OFT ↓ Immobility in FST, not in TST	Lee et al. (2019)
Puerarin	↓ Iba-1+ ↓ COX intensity in microglia	mRNA expression and protein levels: ↓ IL-1β ↓ IL-6 ↓ TNF-α	–	–	↑ DCX+	↑ Sucrose intake ↓ Immobility in FST	Cheng et al. (2019)

(*continued on next page*)

Table 3 (*continued*)

Treatment	Microglia[a]	Pro-inflammation[a]	Anti-inflammation[a]	Proliferation[a]	Differentiation[a]	Depression[a]	Study
Rg1	↓ Iba-1+ (+activated microglia	mRNA expression: ↓ IL-1β ↓ IL-6 ↓ TNF-α (↑ phosphorylation p 65 NF- κB) ↑ iNOS ↑ COX Regulated MAPK pathway.	–	–	↑ DCX+	↑ Social interaction ↓ Immobility in TST and FST	Jiang et al. (2020)
rHMGB1	↓ Iba-1+	mRNA expression: ↓ IL-1 β ↑ HMBG1 ↓ p65 ↓ BIP ↓ XBP1 (ER stress)	–	–	= MAP-2	↑ Social behaviour in SIT = Time in centre or open arm (OFT; EPM)	Liu et al. (2019)
Salvianolic acid B	= Iba-1+ (= Ameboid: larger body and few shorter processes) = CD11b (mRNA expression)	mRNA at 5 weeks: ↓ IL-1β ↓ iNOS ↓ TNF-α mRNA at 6 weeks: ↓ IL-1β ↓ IL-6 ↓ IFN- γ ↓ iNOS mRNA at 7 weeks: ↓ IL-1β ↓ IL-6 ↓ IFN- γ ↓ TNF-α ↓ iNOS Ratios: ↓ IL-1β/IL-1ra ↓ iNOS/Arg-1 ↓ TNF-α/IL-10	mRNA at 6 weeks: ↑ IL-10 ↑ TGF-β mRNA at 7 weeks: ↑ IL-4 ↑ IL-10	= BrdU+	↑ BrdU/DCX+ ↑(BrdU/DCX+)/BrdU + ratio ↑ DCX+ ↑ DCX mRNA = Prolongations in DCX ↑ BDNF ↑ IGF-1	↑ Sucrose intake (= imipramine) ↑ Latency and time of immobilization in FST and TST (= imipramine) ↑ Body weight (= imipramine)	Zhang et al. (2017)

Abbreviations. Arg-1: Arginase 1; ASC: apoptosis-associated Speck-like protein containing a CARD; BBG: Brilliant Blue G; BDNF: Brain-Derived Neurotrophic Factor; BIP: binding immunoglobulin protein; BrdU: Bromodeoxyuridine; CD(11 b, 45, 68, 200, 206): Cluster of Differentiation; CUMS: Chronic Unpredictable Mild Stress; CX3CL1: CX3C chemokine ligand 1; CX3CR1: CX3C chemokine receptor 1; CWIRS: Chronic Water Immersion Restraint Stress; DCX: Doublecortin; EPM: Elevated Plus Maze; ER: Endoplasmic Reticulum; FCPR16: a PDE4 inhibitor; FST: Forced Swimming Test; HMGB: High Mobility Group Box; Iba-1: Ionized calcium Binding Adapter molecule 1; IFN: Interferon; IL: Interleukin; iNOS: Inducible nitric oxide synthase; LPS: Lipopolysaccharide; MAP-2: Mitogen-Activated Protein 2; MS: Maternal Separation; MWM: Morris Water Maze; NeuN: Neuronal Nuclei; NLPR3: Inflammasome; OFT: Open Field Test; P2X7R: P2X purinoceptor 7; PND: Post-Natal Day; Rg1: Ginsenoside Rg1; rHMGB1: recombinant human HMGB1 protein; RSDS: Repeated Social Defeat Stress; SD: Sleep Deprivation; SIT: Social Interaction Test; SPR: Sucrose Preference Ratio; SPT: Sucrose Preference Test; TGF: Transforming Growth Factor; TNF: Tumor Necrosis Factor; TST: Tail Suspension Test; XBP1: X-Box Binding Protein 1; +: Positive cells.

[a] Effects of treatment with respect to stress group.

reuptake, prevented the reduction in the number of microglia induced by CUMS. Moreover, in the DG, citalopram counteracts the effect of stress by reducing the proportion of microglia characterized by the authors as category 2 (Iba-1-expressing cells with thin and highly ramified processes) and increased the number of microglia of category 1 (Iba-1-expressing cells with cellular processes equal to or slightly longer than the diameter of the soma). Citalopram reversed the decrease in the expression of CX3R1 (a receptor involved in the regulation of microglia) (Harrison et al., 1998) induced by CUMS. These effects overlapped with the increase in the numbers of Ki67+ and BrdU + cells observed in animals subjected to CUMS. Although not significantly, citalopram reversed the reduction in the number of DCX + cells induced by CUMS. Nevertheless, citalopram did not reverse the effect of stress on dendritic organization (Vega-Rivera et al., 2020).

Escitalopram, an antidepressant that selectively inhibits serotonin reuptake, reduced the impact of CUMS on the mRNA expression of TNF-α and iNOS but did not have an effect on mRNA expression of Arg-1 or the CD206/Iba-1+ ratio. Therefore, it did not induce a clear effect on the functional status of microglia and their degree of activation. However, this antidepressant reversed the effect of CUMS on the differentiation of the new-born cells, increasing the number of DCX + cells (Zong et al., 2019).

3.7.2.2. Other molecules and compounds: melatonin, FCPR16, iptakalim, N-acetylcysteine and caffeine. Melatonin, a hormone produced by the pineal gland, has been used as a treatment with antidepressant-like properties (Vega-Rivera et al., 2020). This hormone normalized the morphology of microglia expressing Iba-1 in mice exposed to CUMS and increased the number of microglia, which was reduced by stress. Similarly, melatonin normalized the immunoreactivity of CX3CL1 (fractalkine), a protein that binds to the CX3CR1 microglial receptor. As indicated by the authors, the changes in microglia induced by melatonin were consistent with neurogenesis. Melatonin increased the total number of Ki67+ cells and BrdU + cells, tended to reverse the effects of CUMS on the number of DCX + cells and increased the proportion of DCX + cells with a more elaborate dendritic tree in animals subjected to CUMS (Vega-Ribera et al., 2020).

FCPR16 (N-(2-chlorophenyl)-3-cyclopropylmethoxy-4-difluoromethoxy-benzamide) is a novel inhibitor of phosphodiesterase 4 (PDE4), an enzyme that selectively hydrolyses cAMP and is highly expressed in neurons and glial cells (Lakics et al., 2010). Compared to CUMS exposure, FCPR16 decreased the mRNA levels of the TNF-γ and iNOS and increased the mRNA levels of Arg-1 and CD206, increasing the shift in microglial phenotype and the ratio of CD206+ cells to Iba-1+ cells, suggesting, as speculated by the authors, that there was a shift in the functional state of microglia, showing a less activated phenotype. Similarly, FCPR16 reduced the expression levels of TNF-α and IL-1β and increased levels of IL-10, an anti-inflammatory cytokine. Furthermore, both the number of DCX + cells and the protein expression of DCX were increased in FCPR16-treated animals compared to vehicle-treated animals following exposure to CUMS (Zhong et al., 2019).

Iptakalim, a K-ATP channel opener, is a lipophilic para-amino compound that may cross the blood-brain barrier (Zhou et al., 2007) and play an essential role in brain neuroinflammation (Lu et al., 2014). Iptakalim ameliorated the high expression of MAC-1 (CD-11), IL-6 and TNF-α and inhibited the increase in IL-1β secretion induced by CUMS. Iptakalim reversed the effects of CUMS on neural stem cell proliferation and may have had an effect on the fate of new-born neurons in stressed animals, ameliorating the reduction in the number of DXC + cells and β-tubulin III expression (Lu et al., 2014).

Caffeine has also been used to reduce stress-induced depression. Since caffeine reduced the number of $CD68^{+}$ cells in the DG of the hippocampus and the protein levels of both Iba-1 and CD68 in the chronic water immersion restraint stress model, presumably inhibiting microglial activity, this compound may exert pro-neurogenic effects by reducing microglial activity. In fact, caffeine reversed the reduction in the number of BrdU+/DCX + cells in the DG (Mao et al., 2020).

3.7.3. Traditional oriental medicine formulations with antidepressant properties

Twenty-eight days of treatment with *ginsenoside Rg1* (Rg1), the major active ingredient of ginseng, reduced the increase in the neuroinflammatory response induced by chronic social defeat stress. Thus, this treatment normalized the morphology of microglia in the DG and reduced the number of Iba-1+ cells and the mRNA expression of proinflammatory molecules in the hippocampus, specifically TNF-α, IL-6 and IL-1β. Moreover, this treatment reduced the phosphorylation of NF-κB subunit p65. Rg-1 clearly reduced the expression of iNOS and COX-2, reversed the reduction in Sirt1 protein expression induced by stress and the expression of molecules regulated to the MAPK signalling pathway in the hippocampus. Although a causal connection between neuroinflammation and improvements in neurogenesis induced by Rg1 has not been established, this treatment reversed the reduction in neuroinflammation and the decrease in the number of DCX + cells and protein expression of DCX in the DG of the hippocampus (Jiang et al., 2020). Taken together, these data suggest that improvements in neurogenesis may be related to a reduction in microglial activation and, consequently, a reduction in neuroinflammation.

Myelophil is a traditional oriental medicine for the treatment of fatigue-linked disorders composed of 30% ethanol extract of Astragail Radix and Salvied Radic. This compound attenuated the hyperactivation of microglia induced by CUMS, reduced the levels of the inflammatory cytokines TNF-α and IL-1β in the hippocampus and decreased NLRP3 inflammasome activation and hyperactivity of caspase-1. Correspondingly, myelophil reversed the reduction in the number of DCX + cells in the subgranular zone of the hippocampus induced by CUMS (Lee et al., 2019).

Clinical evidence suggests that *kososan*, a traditional Japanese herbal medicine composed of five herbs (Perillae Herba, Zingiberis Rhizoma, Aurantii Nobilis Pericarpium, Glycyrrhizae Radix and Cyperi Rhizoma), has therapeutic effects against inflammation-associated depressive mood (Ito et al., 2006; Nagai et al., 2008). Kososan reversed the effects of chronic social defeat stress on the number of hippocampal Iba-1+ cells and Iba-1+ aggregates in the molecular layer of the hippocampus. Kososan also increased the number of CX3CR + cells in the molecular layer. In contrast to the number of CX3CR1+ cells, it had no effects on NLRP3+ expression in the hilus or SGZ. Kososan significantly rescued the reduction in the number of BrdU and DCX double-positive cells and Ki67+ cells in defeated mice but not the total number of BrdU + cells in the DG (Ito et al., 2017).

Icariin and its metabolite *icaritin* are major constituents of flavonoids isolated from Herba Epmedii, which possess immunoregulatory properties. Both compounds prevented the increase in RAGE protein expression induced by chronic social defeat stress, and interestingly, icaritin increased TLR4 protein expression, while icariin had no effect on TLR4 protein expression. These treatments increased the expression of TNF-α in stressed animals, but icaritin reduced the increase in mRNA IL-1β expression and increased mRNA IL-10 expression in the hippocampi of stressed mice. Opposite effects on the mRNA expression levels of Arg-1 and CD206 were observed after icariin and icaritin treatments in stressed animals, with icariin treatment inducing a reduction in these levels and icaritin treatment causing an increase. Finally, both treatments decreased Iba-1 expression and increased MAP-2 expression (Liu et al., 2019).

Puerarin is an isoflavone that is well-studied due to its antidepressant, neurotrophic and neuroinflammatory properties. Puerarin reduced the increase in the number of Iba-1+ cells induced by CUMS and reduced the inflammatory response, preventing the increase in IL-1β, TNF-α and IL-6 levels. Furthermore, it reversed the effect of stress on the differentiation of new hippocampal cells (Cheng et al., 2019).

Salvianolic acid B is a well-known traditional Chinese herb isolated

from Salvia miltiorrhiza and is frequently used for the treatment of cardiovascular and cerebrovascular diseases. This polyphenolic compound decreased the ratio of (IL-6+-Iba-1+)/Iba-1+ cells, increased the ratio of (Arg-1 ± Iba-1+)/Iba-1+ cells in the hippocampus, and blocked CUMS-induced effects. Given that salvianolic acid B blocked the decrease in the number of BrdU ± DCX + cells in the SGZ of the hippocampus and restored the number of DCX + cells and the gene expression of DCX in the hippocampi of animals exposed to CUMS, it may be possible that anti-inflammatory mechanisms and neurogenic effects, to some degree, functionally overlap. Nevertheless, salvianolic acid B did not affect the length of DCX + cell processes, suggesting, that it had no effect on the degree of CUMS-induced impairment of the maturation of the new hippocampal cells (Zhang et al., 2017).

3.8. Are microglial changes and neurogenic deficits associated with depressive-like behaviours induced by psychological stress?

To answer this question, the effect of treatments that block or palliate the impact of stress on microglia, neuroinflammation and neurogenesis (described in paragraph 3.5) on behaviours associated with depression was determined (Table 3).

3.8.1. Treatments that inhibit microglial changes induced by stress

In early stressed animals, minocycline treatment did not prevent the reduction in social preference in response to chronic social defeat stress (McKim et al., 2016) but reduced the increase in depression score and anxiety-like behaviour induced by maternal separation followed by a second stressor. Regarding depressive-like behaviour, this treatment reduced immobility time in the FST and increased sucrose consumption in the sucrose preference test. Concerning anxiolytic properties, minocycline increased the time spent exploring the centre in the open field test (Han et al., 2019).

In adults stressed animals, chronic treatment with BBG reversed coat deterioration and the impairments in nest-making behaviour induced by CUMS (Farooq et al., 2018), suggesting that it improved the motivational state of animals.

Pre-treatment with rHMGB1 prevented the depressive-like behaviour induced by chronic social defeat stress but not the anxiogenic-like behaviour, as measured using the open field test and elevated plus maze (Liu et al., 2019).

LPS, contrary to expectation, reversed the depression and anxiogenic-like behaviour induced by CUMS. In fact, this toxin increased locomotor activity and the time spent in the centre in the open field test in stressed animals. In CUMS-exposed mice, LPS reduced floating time and increased the latency to first float, suggesting that it has antidepressant properties. LPS did not reverse the decrease sucrose preference or reduction in social interaction induced by CUMS (Kreisel et al., 2014). It must be taken into account that the animals received a single administration of a low dose of the drug (Couch et al., 2016), which also tends to cause adverse effects, increased depression-related behaviours as observed in the control animals.

3.8.2. Treatments with antidepressant properties

3.8.2.1. Antidepressant drugs. Fluoxetine improved depression-like behaviour in response to CUMS (Lu et al., 2014; Farooq et al., 2018) and chronic water immersion restraint stress (Mao et al., 2020) models, improving coat conditions, and alleviating the nest-building deficits induced by CUMS (Farooq et al., 2018), reduced the immobility time in the FST and TST and increased the sucrose intake of animals subjected to chronic water immersion restraint stress in the sucrose preference test (Mao et al., 2020). Additionally, this antidepressant attenuated the anxiogenic behaviour of animals exposed to chronic social defeat stress, as assessed by the open field test and elevated plus maze. Nevertheless, this drug did not reverse the social avoidance induced by chronic social defeat stress (Liu et al., 2019).

Citalopram improved sucrose intake and reduced immobility in the FST, but it had no effect on the coat conditions of animals subjected to the CUMS protocol (Vega-Rivera et al., 2020).

Imipramine improved social interaction and reversed the effect of chronic social defeat stress on sucrose intake and immobility in animals (Jiang et al., 2020). Moreover, this antidepressant reversed the effects of CUMS on sucrose intake and immobility time and increased latency to the first immobility period in the FST and TST (Zhang et al., 2017).

Escitalopram reduced the immobility time in the FST and TST induced by CUMS, increased hedonic behaviour in the sucrose preference test and did not have an effect on mobility in the open field test (Zhong et al., 2019).

3.8.2.2. Other molecules and compounds: melatonine, FCPR16, iptakalim and caffeine. Melatonin protected against stress-evoked depressive phenotypes, increasing sucrose intake, reducing immobility in the FST and improving coat conditions in animals subjected to CUMS (Vega-Rivera et al., 2020).

Melatonin had a marked effect on ameliorating chronic social defeat stress-induced depressive-like behaviours in mice. This treatment improved social interaction and sucrose intake and reduced immobility in the FST, suggesting that it has antidepressant-like properties (Jiang et al., 2020).

FCPR16 decreased immobility time in the FST and TST in animals subjected to CUMS without inducing psychostimulant disturbances. Similarly, it increased the sucrose preference ratio of stressed animals, suggesting that it has antidepressant properties (Zhong et al., 2019).

Iptakalim alleviated depression-like behaviours in animals subjected to CUMS, reducing the immobility time in the FST and TST (Lu et al., 2014).

Caffeine reversed the depressive-like behaviours induced by chronic water immersion restraint stress, reducing immobility time in the FST and TST and increasing preference for sucrose (Mao et al., 2020).

3.8.3. Traditional oriental medicine formulations with antidepressant properties

Ginsenoside Rg1 (Rg1) treatment attenuated chronic social defeat stress-induced depressive behaviours in mice, attenuating the reduction in time spent in the interaction zone in the social interaction test, reversing the decrease in sucrose intake and reducing the increase in immobility in the TST (Jiang et al., 2020).

Myelophil reversed the reduction in total distance travelled in the open field test by animals subjected to CUMS, suggesting that it has anxiolytic properties, and exhibited antidepressant-like activity, reducing immobility time in the FST and TST (Lee et al., 2019).

Kososan reversed stress-induced social avoidance behaviours in mice but did not compensate for the effects of stress on body weight reduction (Ito et al., 2017).

Icariin and icaritin had anxiolytic effects in animals exposed to chronic social defeat stress, increasing the time that animals spent in the centre in the open field test and in the open arms the elevated plus maze, but were unable to reverse the social avoidance induced by social defeat (Liu et al., 2019).

Salvianolic acid B reversed the decrease in sucrose consumption, increased the latency to the first immobility period and reduced the immobility time in the FST and TST induced by CUMS (Zhang et al., 2017).

Puerarin, along with exhibiting pro-neurogenic and anti-inflammatory properties, reversed the development of stress-induced depression-like behaviour (Cheng et al., 2019).

4. Discussion

This systematic review was performed to determine whether stress-

induced microglial changes may be involved in the neurogenesis deficits induced by stress and whether these changes are involved in the development of depressive-like behaviours. To answer this question, we first focused on the depressive symptoms induced by psychological stress. Next, we reviewed the effects of psychological stress on neurogenesis. Then, we focused on microglial and neuroinflammatory changes. Hereafter, we reviewed available evidence on the relationship among stress, microglial and inflammatory and neurogenic changes and finally on the relationship among stress, microglial and inflammatory changes, neurogenic impairments and the development of depression.

4.1. Psychological stress and depressive-like behaviours

The reviewed data indicated that psychological early-life stress induced depressive-like behaviours. Thus, anhedonic behaviour, impaired coping response, increased anxiety behaviour after maternal separation (Han et al., 2019) and loss of body weigh on offspring of mother sleep deprived were observed (Zhao et al., 2014). Cognitive impairments such as spatial memory alterations were also detected after maternal sleep deprivation (Zhao et al., 2014).

Psychological stress during adulthood also induced depressive-like behaviours. In this sense, anhedonic behaviour and reduced motivation were observed after exposure to CUMS (Cheng et al., 2019; Farooq et al., 2018; Kreisel et al., 2014; Lu et al., 2014; Rimmerman et al., 2017; Vega-Ribera et al., 2020; Zhang et al., 2017; Zhong et al., 2019), chronic social defeat stress (Jiang et al., 2020) and chronic water immersion restraint stress (Mao et al., 2020). CUMS induced fatigability (Farooq et al., 2018). An impaired coping response to stress, as measured by the FST or TST, was observed after exposure to CUMS (Cheng et al., 2019; Kreisel et al., 2014; Lee et al., 2019; Lu et al., 2014; Vega-Ribera et al., 2020; Zhang et al., 2017; Zhong et al., 2019), chronic social defeat stress (Jiang et al., 2020) and chronic water immersion restraint stress (Mao et al., 2020). CUMS (Kreisel et al., 2014; McKim et al., 2016) and chronic social defeat stress (Ito et al., 2017; Jiang et al., 2020; Liu et al., 2019) affected social behaviour. Moreover, body weight was reduced after exposure to chronic social defeat stress (Ito et al., 2017), sleep deprivation (Wadhwa et al., 2017), chronic water immersion restraint stress (Mao et al., 2020) and CUMS (Lu et al., 2014; Zhang et al., 2017), although not consistently (Vega-Ribera et al., 2020). Animals exposed to CUMS (Kreisel et al., 2014; Lee et al., 2019; Zhong et al., 2019), and chronic social defeat stress (Liu et al., 2019) exhibited significantly increased anxiety-like behaviour, an impairment closely linked to depression. Psychological stress also produced cognitive alterations. It was observed that chronic social defeat stress induced impairment in rule acquisition in a working memory task (McKim et al., 2016); that chronic social defeat stress (McKim et al., 2016), F (Wadhwa et al., 2017) induced spatial memory alterations; and that CUMS altered recognition memory (Rimmerman et al., 2017).

However, it is worth noting that most of the works included in this review examined the effect of stress on motivational and emotional behaviour as a measure of depressive-like symptoms. In contrast, while it was shown that cognitive impairments contribute to sustained disability during depressive disorders, there were far fewer studies designed to study depression-induced cognitive impairment. Cognitive symptoms associated with depression significantly impact patients' function and quality of life, increasing the risk of depression recurrence. Accumulating evidence has linked neuroinflammation to cognitive impairments (Pfau et al., 2016). Moreover, current hypotheses about the role of new-born neurons in brain function and behaviour focus on their contribution to specific facets of cognition and behaviour (Gonçalves et al., 2016). The neurogenic and neuroinflammatory effects of stress are well-known, but in the studies revised here, its cognitive consequences have been poorly examined. Only four of the studies included in the present review focused on cognitive impairment induced by stress, especially spatial memory impairment. In the same way, depression is associated with motor symptoms that may have clinical and therapeutic implications for treatment, but the effects of stress on locomotor activity, like cognition, have scarcely been explored beyond the assessment required for the interpretation of psychological tests.

In summary, in studies aimed at examining the relationship between stress, microglia, neurogenesis and depression, anhedonia and passive coping strategies in response to inescapable stress are the most commonly explored symptoms after exposure to chronic stress. However, cognition, fatigability, and motor symptoms, which may have clinical and therapeutic implications for treatment, have been scarcely studied. However, it is clear that psychological stress induces depression-like behaviour.

4.2. Psychological stress and hippocampal neurogenesis

A large body of evidence has demonstrated the importance of the hippocampus for emotional behaviour (Barkus et al., 2010; Zhu et al., 2019). Newly generated neurons are strongly believed to contribute to emotional regulation and dynamically regulate stress reactivity (Snyder et al., 2011), but the hippocampus is also a target of stress (Orlovsky et al., 2014). The majority of studies suggest that stress negatively impacts adult neurogenesis by suppressing it, but there are some exceptions. The negative impact of stress on neurogenesis is due to, at least partially, increased circulating levels of endogenous glucocorticoids (Pariante and Lightman, 2008; Anacker et al., 2011; Provençal et al., 2020). The effects of stressful experiences differ depending on the stage of adult neurogenesis (i.e., cell proliferation, neuronal differentiation, and cell death) (Bain et al., 2004; Heine et al., 2004; Malberg and Duman, 2003; Pham et al., 2003), as well as the context of the stressor that is applied. Adult new-born neurons undergo multiple developmental stages before becoming functionally integrated into the hippocampal circuitry. As reviewed above, the overall body of literature examining the effect of stress on neurogenesis indicates that psychological stressors affect different steps of this process. Data have revealed that, in most cases, stress in both early-life (Han et al., 2019) or in adult (Ito et al., 2017; Jiang et al., 2020; Lu et al., 2014; Vega-Ribera et al., 2020; Wadhwa et al., 2017) affects proliferation. However, no effect on proliferation has been observed after exposure to or maternal sleep deprivation (Zhao et al., 2014), CUMS (Kreisel et al., 2014; Zhang et al., 2017), chronic social defeat stress (McKim et al., 2016). Since opposing effects have been observed both after stress applied in early developmental and adult periods, the time in the life cycle when the stressor is applied seems not to be so relevant to explain differences in proliferation. Most likely, methodological differences, such as different thymidine analogue administration protocols, or differences in mouse strains, may explain, at least in part, these apparent inconsistencies. Thus, proliferative activity may be different in different mouse strains (Kemmperman et al., 1997). Different CUMS or chronic social defeat stress protocols have been used between studies as well (Ito et al., 2017; McKim et al., 2016). Moreover, dilution after division may hinder BrdU labelling in such cells (Mandyam et al., 2007). Labelling of proliferating cells with BrdU also depends on penetration of the targeted cells with a uniform concentration of the compound (Wojtowicz and Kee, 2006). Due to variations in the amount of BrdU that penetrates cells and the use of different protocols of administration, the probability of obtaining conclusive findings decreases. The use of Ki67 as a marker for cell proliferation (Wojtowicz and Kee, 2006) may be an alternative strategy for confirming the effect of stress on cell proliferation (Ito et al., 2017; Vega-Rivera et al., 2020; Wadhwa et al., 2017). The results of the three reviewed studies that used Ki-67 were consistent, revealing a negative effect of stress (CUMS, chronic social defeat stress and sleep deprivation) on cell proliferation (Ito et al., 2017; Vega-Rivera et al., 2020; Wadhwa et al., 2017). The involvement of glucocorticoid receptors in this process may not be ignored either. Activation of these receptors, which depend in part on circulating glucocorticoid levels, can have different effects on proliferation. Thus, low cortisol concentrations predominantly activate MR, while high concentrations of cortisol (or corticosterone for animals)

also activate GR. Animal studies, together with human cellular data, support the notion that MR- and GR-activation exert opposite effects on progenitor proliferation (Anacker et al., 2013a). These competing effects may be responsible for some of the inconsistencies between studies on the effects of stress on cell proliferation.

On the other hand, only two studies assessed the effect of stress on survival, and these studies revealed that both CUMS and chronic social defeat stress reduced the survival of new cells (Ito et al., 2017; Vega-Rivera et al., 2020). In contrast, all studies that have valuated the effect of stress on the differentiation of new hippocampal cells concluded that psychological stress in both early period (Han et al., 2019; Zhao et al., 2014) or in adult (Cheng et al., 2019; Ito et al., 2017; Jiang et al., 2020; Lee et al., 2019; Liu et al., 2019; Lu et al., 2014; Mao et al., 2020; McKim et al., 2016; Rimmerman et al., 2017; Vega-Ribera et al., 2020; Wadhwa et al., 2017; Zhang et al., 2017; Zhong et al., 2019) affects this phase of neurogenesis. This congruence between studies could be due to the fact that, unlike cell proliferation, both MR and GR activation decreases cell neuronal differentiation (Anacker and Pariante 2012; Anacker et al., 2013a).

The findings related to the effect of stress on the maturation of new neurons were also inconsistent, reporting that chronic social defeat stress (McKim et al., 2016) and CUMS (Zhang et al., 2017) have no effect on or affect the degree of maturation (Vega-Ribera et al., 2020). Different criteria have been used to determine the degree of maturity, which may partially explain the differences in results.

In summary, psychosocial stress affects the proliferation, survival and differentiation of hippocampal NPCs. Considering the results of studies selected in this review, it is essential to take into account the species used, the timing, the thymidine analogue administration protocol, the design of the experiment used to assess how stress impacts neurogenesis and the procedures used to quantify neurogenic changes (Table 1).

This alteration in neurogenesis due to stress may in turn impact on neurobiological mechanisms of stress regulation. In this sense, reduced neurogenesis may impair hippocampal inhibitory control over the HPA axis during stress, subsequently causing sustained hypercortisolemia and depressive symptoms (Anacker and Pariante 2012; Anacker et al., 2013a,b).

4.3. *Psychological stress and microglial changes*

Factors that affect neurogenesis play an essential role in regulating emotion and mood and contribute to the neuropathology of depression (Serafini et al., 2014; Zhang et al., 2017). One of the key factors that may regulate neurogenesis is microglia. These resident macrophages in the nervous system may coordinate the brain inflammatory response (Díaz-Aparicio et al., 2020), through which they regulate the neurogenic response to stress. In the hippocampus, increased microglial activation after exposure to stress, which may be induced by an increase in glucocorticoid levels (Yirmiya et al., 2015), has been associated with reduced neurogenesis (Mao et al., 2020). Chronic psychological stress, which induces depressive-like symptoms, impacts microglial morphology, number, and function. Extensive evidence has documented that exposure to chronic psychological stress may induce microglial overactivation (Frank et al., 2016; Ramirez et al., 2017; Stein et al., 2017). Nevertheless, while studies using early life stress as sleep deprivation, and maternal separation or adult stress as chronic social defeat stress, chronic water immersion restraint stress, support this idea, some, though not all, studies using CUMS have reported contradictory results. In fact, using a similar procedure (i.e., CUMS), an increase in the number of microglia (Cheng et al., 2019) with ameboid shapes (Lee et al., 2019; Zhang et al., 2017), a reduction in the number of microglia with an increase in soma area (Vega-Ribera et al., 2020) and even a reduction in the number of microglia with dystrophic morphology (Kreisel et al., 2014) have all been observed (Table 2). In contrast, other protocols, including maternal separation (Han et al., 2019) or stress in the adult period such as chronic social defeat stress (Ito et al., 2017; Jiang et al., 2020; Liu et al., 2019; McKim et al., 2016), chronic water immersion restraint stress (Mao et al., 2020), 48 h of sleep deprivation (Wadhwa et al., 2017) and maternal sleep deprivation (Zhao et al., 2014), induced an increase in microglia number, with an increase in soma size and thickening of cellular processes (Jiang et al., 2020; McKim et al., 2016; Wadhwa et al., 2017; Zhao et al., 2014) being the primary morphological changes. These apparently inconsistent findings related to the microglial response observed after CUMS can most likely be attributed to differences in the procedures applied (Table 2). Individual differences are crucial for assessing the negative consequences of stress experiences. Different strains of mice (C57BL/6 J versus BALB), animals of different ages (from 7 to 24 weeks old) and varying CUMS protocol durations (from 3 to 8 weeks) have been used. Indeed, the C57BL/6 J line appears to be less susceptible to stress than the BALB strain (Dadomo et al., 2010; Razzoli et al., 2010a, 2010b). Moreover, prolonged stress induces greater activation of microglia in young animals than in old animals (Park et al., 2011). Finally, due to the bi-directional impair of microglial status, after a highly stressful protocol, initial proliferation and activation followed by a decline and suppression of microglial function may be observed (Kreisel et al., 2014).

Overall, this systematic review revealed that the effects of chronic stress on the activation of hippocampal microglia are heterogeneous and depend on several parameters, such as the nature of the stress regimen, duration of the stress procedure, age of the animals, and animal strain. However, it is intriguing to note that this may be interpreted as a dynamic transition between the activation and decrease of microglia (Kreisel et al., 2014). Furthermore, the involvement of other variables cannot be ruled out. However, there is no doubt that stress impairs microglial status and modifies the expression of cytokines and chemokines by tipping the balance in favour of inflammation. Given that microglia are the primary source of proinflammatory and immune regulatory cytokines in the brain (Kreisel et al., 2014; Lehmann et al., 2018), which may induce a toxic environment in the brain under certain conditions (Lehmann et al., 2018), impaired microglial status may be the cause of the inflammatory imbalance induced by stress. In fact, psychological stress leads to activation of the inflammatory cascade, resulting in an increase in the levels of proinflammatory cytokines and a reduction in the levels of anti-inflammatory cytokines. In this sense, psychological stress is now widely accepted as an important trigger of inflammation and a major contributor to symptoms of chronic inflammatory disease (Pace et al., 2009; Rohleder, 2014; Steptoe et al., 2001; Weik et al., 2008). These effects may be triggered, at least partially, by glucocorticoid action. While it is evident that exogenous glucocorticoids exert anti-inflammatory effects in a vast number of inflammatory conditions (Boumpas et al., 1993), in situations of chronic psychosocial stress glucocorticoid down-regulation occurs, leading to an increase of the duration and/or intensity of the inflammatory response (Cohen et al., 2012). The effect was also dose dependent, only occurring for intermediate (stress-relevant) concentrations of glucocorticoid (Horowitz et al., 2020) One of the mechanisms by which glucocorticoids induce neuroinflammation is through their microglial receptors (Feng et al., 2019).

Changes in the status of microglia, which entail an imbalance between proinflammatory and anti-inflammatory cytokines, may lead to changes in neurogenesis and therefore long-term impairments in mood, cognition, and behaviour (Chesnokova et al., 2016; Monje et al., 2003; Parnet et al., 2002). Indeed, most psychological stressors that disrupt neurogenesis induce symptoms that are reminiscent of either anxiety or depression (Han et al., 2019; Ito et al., 2017; Jiang et al., 2020; Lee et al., 2019; Liu et al., 2019; Lu et al., 2014; Mao et al., 2020; McKim et al., 2016 Rimmerman et al., 2017; Vega-Rivera et al., 2020; Wadhwa et al., 2017; Zhang et al., 2017; Zhao et al., 2014; Zhong et al., 2019). Determining whether cytokines are collectively dysregulated in stressed animals in response to psychological stress as part of a broader pro- and/or anti-inflammatory immune response or whether specific cytokines are

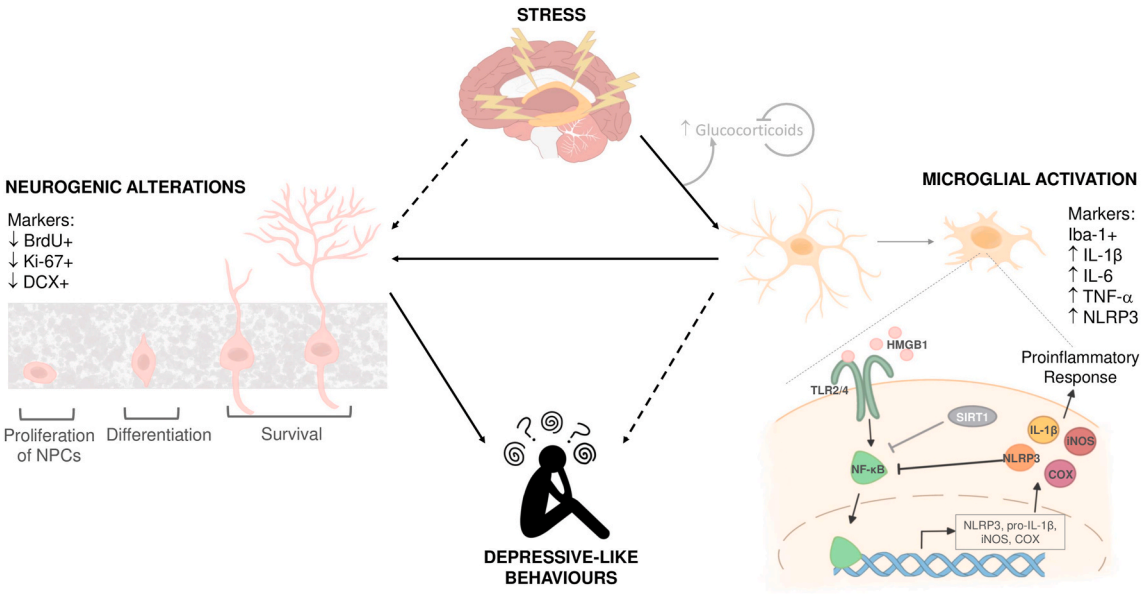

Fig. 3. Schematic representation of the cascade of inflammatory events induced by psychosocial stress and involved in the development of depression. The most relevant markers of inflammation and neurogenesis used in the reviewed studies are indicated. In addition, neurogenic processes and the inflammatory response pathway are specified. Additionally, we also include SIRT1, an important member of the sirtuin family, induces deacetylation of the NF-kB subunit p65, thereby inhibiting its activity. Continuous arrows represent a direct relation, and discontinuous arrows and indirect relation.

dysregulated during the varying stages of stress in the case of chronic stress is crucial for characterizing the impact of stress on neurogenesis.

4.4. Psychological stress and molecular factors associated with inflammation

The cascade of inflammatory events induced by stress may be triggered by several factors (Fig. 3), one of which is high mobility group protein box 1 (HMGB1). When this alarmin is translocated from the nucleus to the cytoplasm or to the extracellular medium, it may act as a damage-associated molecular pattern (DAMP), impairing nearby cells and inducing neuroinflammation (Scaffidi et al., 2002). Stress exposure may induce the translocation of HMGB1 from the nucleus to the cytoplasm and microglial release of HMGB1 in the hippocampus, which in turn increases expression of NF-κB (Weber et al., 2015) through Toll-like receptors (TLRs) TLR2 and TLR4 (van Zoelen et al., 2009). Activation of the TLR2 and TLR4 receptors induces an increase in microglial activation and strengthens proinflammatory response. Activation of NF-κB by phosphorylation, a key transcription factor controlling proinflammatory signal transduction, has also been linked to the inflammatory response mediated by microglia and may also be involved in cytokine priming induced by stress. Thus, activation of NF-κB may result in neuronal injury and apoptosis, affecting the transcription of many proinflammatory cytokines and neurotoxic factors, including COX2 and iNOS (Sethi et al., 2008). NF-κB induces activation of the nod-like receptor protein 3 (NLRP3) inflammasome (reviewed in Kelley et al., 2019), a multimeric protein complex that initiates an inflammatory response and cellular death, triggering release of the proinflammatory cytokines IL-1β and IL-18 (Yang et al., 2019). At the same time, the NLRP3 inflammasome may regulate stress-induced NF-κB protein complex activation in a depression mouse model (Su et al., 2017; Wang et al., 2020). IL-1β is seen as the "orchestra conductor" of inflammation because it is a strong signal that stimulates the production of other inflammatory molecules (Basu et al., 2004). In addition, SIRT1, an important member of the sirtuin family, induces deacetylation of the NF-κB subunit p65, thereby inhibiting its activity (Xie et al., 2013; Yoshizaki et al., 2009) (Fig. 3).

Psychosocial stress can trigger the inflammatory response, although studies have focused on a few steps of the inflammatory cascade chronic social defeat stress increases cytoplasmic expression of HMGB1 (Liu et al., 2019), which triggers the inflammatory response through the HMGB1-TLR2/4-NF-κB signalling pathways (Liu et al., 2019). There is also evidence that chronic water immersion restraint stress modulates this pathway (Mao et al., 2020). The remaining studies focused on the subsequent steps of the neuroinflammatory cascade.

Other studies have focused on the effects of stress on the expression of pro- and anti-inflammatory cytokines. Given that IL-1β is one the first cytokines involved in the hierarchical cytokine signalling cascade in the central nervous system (Basu et al., 2004) the results of most of the studies reviewed here, suggested that psychological stress, irrespective of stress condition, increased neuroinflammation (Cheng et al., 2019; Han et al., 2019; Jiang et al., 2020; Lee et al., 2019; Liu et al., 2019; Lu et al., 2014; Mao et al., 2020; McKim et al., 2016; Wadhwa et al., 2017; Zhang et al., 2017; Zhong et al., 2019) An increase in the level of IL-1β would be followed by an increase in the levels of other cytokines and chemokines. In fact, increased levels of proinflammatory cytokines and chemokines or reduced levels of anti-inflammatory cytokines have also been observed in response to different stressors (Cheng et al., 2019; Han et al., 2019; Ito et al., 2017; Jiang et al., 2020; Lee et al., 2019; Liu et al., 2019; Lu et al., 2014; Mao et al., 2020; McKim et al., 2016; Wadhwa et al., 2017; Zhang et al., 2017; Zhao et al., 2014; Zhong et al., 2019). With some exceptions, studies have primarily focused on assessing mRNA levels, which do not always correlate with protein levels (Koussounadis et al., 2015) this could at least partially explain these discrepancies.

Taken together, these results indicate that stress is associated with an increased neuroinflammatory profile characterized by an increase in proinflammatory cytokine and chemokine levels and a reduction in anti-inflammatory cytokine levels. Some studies have found the opposite effect. But due to the limited number, more studies are needed in the future to determine what mechanisms might be mediating these seemingly contradictory results.

4.5. Psychological stress affects the interaction between microglia and neurogenesis and the development of depressive-like behaviours

Alterations in the morphofunctionality of microglia coincide with neurogenic alterations (Sierra et al., 2014; reviewed in Vega-Rivera et al., 2020) and depressive-like behaviours (Yirmiya et al., 2015; Zhang

et al., 2018). Indeed, in the reviewed studies, microglial impairment and neuroinflammatory signalling were shown to be temporally associated with or coincide with neurogenetic disruptions in the DG of the hippocampus. Nevertheless, it could be questioned whether the impact of stress on neurogenesis and, in turn, on behaviour specifically results from microglial changes or is temporally associated with separate processes. Approaches using specific microglial manipulation are useful for improving the understanding of the mechanism underlying the reduction in stress-induced neurogenesis and its connection to depression. Pharmacological approaches that directly or indirectly modify the activation status of microglia have been used. Collectively, the results shown in Table 3 indicate in general that both direct and indirect pharmacological strategies modify microglial status, reduce neuroinflammation, reverse the impact on neurogenesis and alleviate some depressive-like behaviours, although some inconsistencies have been noted. In fact, different drugs that modulate microglial activity in different ways have shown a similar ability to rescue the stress-induced deficits in proliferation rate or differentiation state (Table 3). Nevertheless, these effects have not been universally observed. Prevention of neurogenesis impairments and/or reversion of depressive-like behaviour induced by stress are not always directly associated with microglial changes; therefore, the relationship between increased neurogenesis and improvements in mood disorders is sometimes inconsistent. In this sense, some treatments that suppress microglial activation during the first few days of stress exposure have minimal or no effects on neurogenesis. For example, treatment with BBG, a P2X7 receptor antagonist that directly acts on microglial activation, prevents the effect of stress on depressive-like behaviour but does not reverse the effects of CUMS on DCX + cell number (Farooq et al., 2018). Similar results were observed in an experiment involving pre-treatment with rHMGB1. This treatment was shown to positively impact microglial changes and alleviate depressive-like behaviour induced by chronic social defeat stress but have no effect on MAP-2 expression. Moreover, rHMGB1 cannot prevent the anxiogenic effects of chronic social defeat stress (Liu et al., 2019). In addition, treatment with minocycline, which has been shown to markedly reduce microglial changes induced by stress, has no effect on the maturation of new-born neurons. Regarding the behavioural effects of this treatment, both an improvement in Barnes maze performance and an absence of an effect on social interaction have been observed (McKim et al., 2016). Likewise, salvianolic acid B, which has no effect on microglial morphology and CD11b expression, prevents the impact of stress on cell differentiation and on the development of depressive symptoms (Zhang et al., 2017). This effect is probably mediated by a reduction in the pro-inflammatory microglial phenotype. Variations in the reports of the effects of microglial modulation on social defeat stress further complicate this phenomenon; some studies have demonstrated that microglial modulation has significant positive effects on social interactions (Ito et al., 2017; Jiang et al., 2020), while others have not observed such effects (Liu et al., 2019; McKim et al., 2016). Furthermore, no effect of the treatments on motor parameters in the implemented tests was observed (Zhong et al., 2019).

Although the mechanisms underlying the different effects of treatments that modulate microglia are presently unknown, several hypotheses can be proposed. These apparently inconsistent findings can most likely be attributed to differences in the procedures applied, such as different protocols of administration, indicating the necessity of studies on the effect of the pharmacological modulation of microglial activation, as shown here. Thus, treatments that were shown to positively reverse the social interaction deficit induced by chronic social defeat stress were administered during and for a few days following the defeat procedure (Ito et al., 2017; Jiang et al., 2020). Moreover, differences in methodologies and strains used may be associated with the discrepancies among these studies (Ito et al., 2017; Jiang et al., 2020; Liu et al., 2019; McKim et al., 2016). Most likely, when a more prolonged or intense chronic social defeat stress protocol is used, different mechanisms that underlie social interaction deficits as well as those underlying changes in neurogenesis, may be involved. Therefore, treatments focusing on additional therapeutic targets are necessary to prevent their effects. Regarding to motor changes, mechanisms other than microglial and neurogenic changes in the hippocampus may be involved. Further studies are needed to test these hypotheses. Finally, differences in the markers used to assess different phases of neurogenesis may explain the inconsistencies noted between some studies.

In summary, it is widely documented that stress induces depressive-like behaviour. Unambiguously, the current review supports these findings. These alterations did not depend on the time of life at which the stress protocol was applied. It is worth noting that, while there has been much research on emotional symptoms resulting from stress, few of the studies examined in this systematic review have focused on cognitive impairment induced by psychological stress. On the other hand, there is extensive evidence that exposure to chronic psychological stress may induce microglial changes (Cheng et al., 2019; Farooq et al., 2018; Han et al., 2019; Ito et al., 2017; Jiang et al., 2020; Kreisel et al., 2014; Liu et al., 2019; Lu et al., 2014; McKim et al., 2016; Rimmerman et al., 2017; Vega-Ribera et al., 2020; Zhang et al., 2017; Zhong et al., 2017). However, this systematic review revealed that the effects of chronic stress on microglial activation are heterogeneous and depend on several parameters, such as the nature of the stress regimen, duration of the stress procedure, and animal age or strain. Regarding the inflammatory response to stress, the results of the studies reviewed here indicate a more consistent pattern of alterations. Psychological stress disrupts homeostasis, shifting immune signalling towards a proinflammatory state. Thus, when microglial changes are induced by stress, an increase in proinflammatory cytokine and chemokine expression and a reduction in anti-inflammatory signalling are observed. This proinflammatory status is associated with or coincides with impaired neurogenesis, with differentiation of the new-born cells being the most studied event related to neurogenesis in the reviewed articles and the most frequently identified alteration. Finally, as noted above, data primarily from studies that used strategies to inhibit or attenuate microglial changes induced by stress may indicate a tantalizing connection among changes in microglial status, neuroinflammation, neurogenesis and the development of depressive-like behaviour. Taken together, the literature on the effects of treatments that modulate the effect of stress on microglia revealed that these four variables of interest, i.e., stress, microglial changes, neurogenesis and depression, may be related (Fig. 3). Numerous studies have used varying types of psychosocial stressors, specifically those that modify microglial activity, impact NPC proliferation and especially differentiation, and induce different depressive-like behaviours. However, some inconsistencies were also found, although the proportion of these inconsistencies was relatively small. On the other hand, we cannot ignore the fact that stress can have an impact on neurogenesis mediated by the action of glucocorticoids (Provençal et al., 2020; Anacker et al., 2013a, 2013b) and the effect on neurogenesis may differ depending on glucocorticoid levels (Anacker et al., 2013a).

Finally, although it is not the aim of this review, it is worth noting that our review also highlights the imbalance in the use of male and female animals. Indeed, virtually all experiments in this area were performed on male animals only; therefore, there is a sex bias in the results. Given that depression is more prevalent in women (Albert, 2015), studies on the neurobiological mechanisms underlying the effect of stress on depression should be designed to use samples that adequately represent the population to adequately answer research this topic. The conclusions drawn from these studies are therefore only partial and should be interpreted with caution.

Taken together, the data analysed here, although not entirely conclusive, seem to suggest that microglial changes induced by psychological stress are affect the regulation of neurogenesis and in turn may be responsible for the development of depressive-like behaviour, but other factors that affect the response to these stressful experiences should not be dismissed. Therefore, additional studies are needed to determine what other factors may mediate this relationship. Identifying

components of biological contexts that are conducive to depressive-like problems induced by stress may help elucidate the strong but poorly understood association between stress and depression and aid the development of effective preventive and therapeutic approaches.

Autor contribution

Conceptualization: CP and MP-M; Data curation: AN-Q; PC-P; MP-M; CP; Formal analysis: AN-Q; Funding acquisition: CP; Methodology: AN-Q; PC-P; Project administration: CP; Supervision: M.P-M; LJS; CP; Validation: MP-M; LJS; CP; Writing - original draft: CP and MP-M; Writing - review & editing: MP-M; AN-Q; PC-P; LJS; CP.

Declaration of competing interest

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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