REVIEW

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Current understanding of the neurobiology of major depressive disorder

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Abstract

Depression is highly prevalent worldwide and associated with significant morbidity and mortality. Approximately 340 million people worldwide suffer from depression at any given time. Based on estimates from the *World Health Organization* (WHO), depression is responsible for the greatest proportion of burden associated with non-fatal health outcomes and accounts for approximately 12% total years lived with disability. Probably no single risk factor can be completely isolated in major depressive disorder (MDD), as interactions between many sources of vulnerability are the most likely explanation. Buttressing the identification of grief, demoralization, hopelessness and styles of psychological coping of the depressed patient are vital, ongoing scientific developments that flow from an increased understanding of this interplay amongst the immune system, endocrine system and brain. The rapidly accumulating body of neurobiological knowledge has catalyzed fundamental changes in how we conceptualize depressive symptoms and has important implications regarding the treatment and even prevention of depressive symptoms in patients.

Keywords: depression, neurobiology, risk factors.

Introduction

Major depressive disorder (MDD) is a complex and inhomogeneous illness with an etiopathogenesis that is based upon multiple factors that may act at different levels (psychological, biological, genetic and social). Mechanisms involved in the emergence of depressive episodes are multifactorial and not yet fully understood [1]. As pointed out, a comprehensive etiological understanding of depression will require the integration of multiple explanatory perspectives [2]. If we want to shed light on the complex interactions between the pathophysiology of depression, its treatment and its cure, we need to consider all the different psychopathological subtypes, the contribution of different neurobiological and psychosocial etiopathogenetic factors, the clinical response to treatment and the long-term prognosis and, additionally, the comorbidity with other psychiatric or somatic disorders. There is enormous variation between individual patients with regard to these different factors, which corresponds to the variability of outcome regarding the time course of response and remission [3].

Changes in the neurobiological substrates of emotional processing before and after antidepressant treatment may be a putative endophenotype for early response and a measurement of these changes can be an indicator for early antidepressant response [4, 5]. There is consistent evidence that patients with depression exhibit biases in attending to, interpreting and remembering negative emotional stimuli congruent with their mood state [6, 7]. In addition, there is evidence that antidepressants are associated with acute changes in how people process emotional stimuli and these effects precede any perceived benefit to mood [8].

Environmental and genetic factors

Severe stressful life events seem to be more deleterious for subjects who have a family history of mood disorders, often referred to as the "stress diathesis" theory of MDD [9]. The proportion of total variance in a trait due to genetic variation (the heritability) for MDD has been estimated from twin studies at 37% [10]. This suggests that while genetic factors play a significant role, MDD cannot be considered a genetic disorder – two-thirds of the factors involved are not explained by genetic variability [11].

Support for the gene-by-environment interaction model in triggering a major depressive episode comes from several large cohort studies, including one where the classic candidate gene in MDD (the gene coding for the serotonin transporter – 5-HTT) was indeed involved in the occurrence of a new episode of depression, but depended on the number of stressful life events the patients had in the previous three months [12]. This approach has received growing attention with the emergence of "epigenetics".

However, major depression can also arise without any prior life event and the vast majority of people experiencing life events do not develop depression. One reason for this might be that the impact of life on the development of an illness may be moderated by a gene-environment interaction. In 2003, Caspi *et al.* prospectively investigated why life events lead to depression in some people but not in others [12]. In a representative birth cohort of 1037 children who had had comprehensive psychiatric assessments at the ages of 3, 5, 7, 9, 11, 13, 15, 18 and 21 years, a functional polymorphism of the promoter

region of the serotonin transporter gene (5-HTT) was found to moderate the influence of stressful life events on depression [12]. Specifically, the study revealed three major results:

▪ With regard to the gene-environment interaction, it was found that life events after the 21st birthday significantly predicted a new onset of depression at age 26 among carriers of an S-allele who had no history of prior depression, but did not predict onset of depression among l/l homozygotes.

▪ Even suicide ideation, which is always susceptible to having an underlying biological mechanism, could be significantly predicted for individuals with the S-allele but not for l/l homozygotes.

▪ Childhood maltreatment during the first life decade also significantly predicted adult depression among S-allele carriers but not among l/l homozygotes.

In addition, the sole relationship between genotype and depression not associated with a life event was not significant. In summary, this model further supports the concept that genetic variants with a high prevalence in the general population probably act to "promote an organism's resistance to environmental pathogens" [12].

Among the several methods by which experience can produce long-lasting changes in protein availability and function, there has been considerable interest in how epigenetic modifications could explain part of the pathophysiology of depression and antidepressant action [13]. Epigenetic changes offer a mechanism by which environmental experiences can modify gene function in the absence of DNA sequence changes. Epigenetics has therefore been invoked to explain several aspects of depression, including high discordance rates between monozygotic twins, the role of maltreatment during childhood, individual differences among inbred rodents, the chronic relapsing nature of the illness and the strikingly greater prevalence of depression in women [14]. Individual differences in neurobiological substrates may explain personality and emotionality styles, which may partly explain higher risk for depression when facing environmental challenges, suggesting a mediator role of vulnerability genes [15].

Epigenetics concerns all induced modifications of gene expression (it is therefore different from variation of gene sequence), explaining how some genes are being transcribed (producing mRNA and them proteins) and other are transcribed less or even not at all. Access to the gene for the transcription process can be decreased (*i.e.*, epigenetic regulation), either through the addition of a methyl radical in certain parts of the gene (CpG islands) or a modification of proteins (histones) around which the DNA winds [16]. Other mechanisms are also important, but are not yet fully understood.

DNA methylation (of cytosine), the first process, seems to be important in the influence of maternal behavior of adult emotional processing [17]. Adult offspring of rats born to mothers with low rates of maternal licking and grooming show an increased anxiety and reduced expression of glucocorticoid receptors within the hippocampus compared with offspring of mothers with high rates of maternal behaviors [18]. Histone acetylation, the second type of epigenetic regulation, is associated with transcriptional activation and decondensed chromatin and seems to be a key substrate for antidepressant action [19]. Increased histone acetylation at the promoter for brain-derived neurotrophic factor in the hippocampus was shown to be required for the ability of chronically administered imipramine to reverse certain deleterious effects of social defeat [20]. Dystrobrevin binding protein 1 (Dysbindin, DTNBP1), widely expressed at significant levels within cerebral cortex and hippocampus was not associated with clinical phenotypes of MDD in limited power analysis [21].

Neural circuitry and neurotransmitters

Several prefrontal and limbic structures and their interconnected circuits have been implicated in affect regulation, including the ventromedial prefrontal cortex, lateral orbital prefrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, ventral striatum (including nucleus accumbens), amygdala and the hippocampus. These regions regulate learning and contextual memory processes, executive function, emotion and reward and have been implicated in depression and antidepressant action [22].

In patients with MDD, regional blood flow studies suggest hyperactivity in the ventromedial prefrontal cortex (which mediates pain, aggression, sexual functioning and eating behaviors) and lateral orbital prefrontal cortex (which assesses risk and modulates maladaptative and perseverative affective states) and hypoactivity in the dorsolateral prefrontal cortex (which maintains executive function, effortful sustained attention and working memory processes) [23]. Using functional MRI paradigms, connectivity studies also suggest a decrement in the "communication" between amygdala and anterior cingulate cortex regions, explaining a decreased capacity of the cortex to regulate subcortical areas mediating negative emotions, usually referred to as a deficit in "top-down" control [20].

Activity within the amygdala and subgenual cingulate cortex is strongly correlated with dysphoric emotions. The nucleus accumbens, a striatal subregion, is important for reward and for hedonic deficits in depression. These forebrain networks are significantly modulated by monoamine projections from midbrain and brainstem nuclei [dopamine (DA) from the ventral tegmental area, serotonin 5-HT from the dorsal raphe in the peri-aqueductal grey area and norepinephrine from the *locus coeruleus*] (Figure 1). In addition to controlling alertness and awareness, these neurotransmitters modulate the salience of emotional stimuli [13].

Magnetic resonance images (MRI) of the brains of patients with depression has identified differences in both structure and function compared to non-depressed subjects. Although some inconsistency exists, meta-analysis have confirmed smaller hippocampal volumes [24]. The loss of hippocampal neurons correlates with impaired memory and dysthymic mood. Drugs that increase serotonin levels in the brain may stimulate neurogenesis and increase the total mass of the hippocampus. This then helps to restore mood and memory [25].

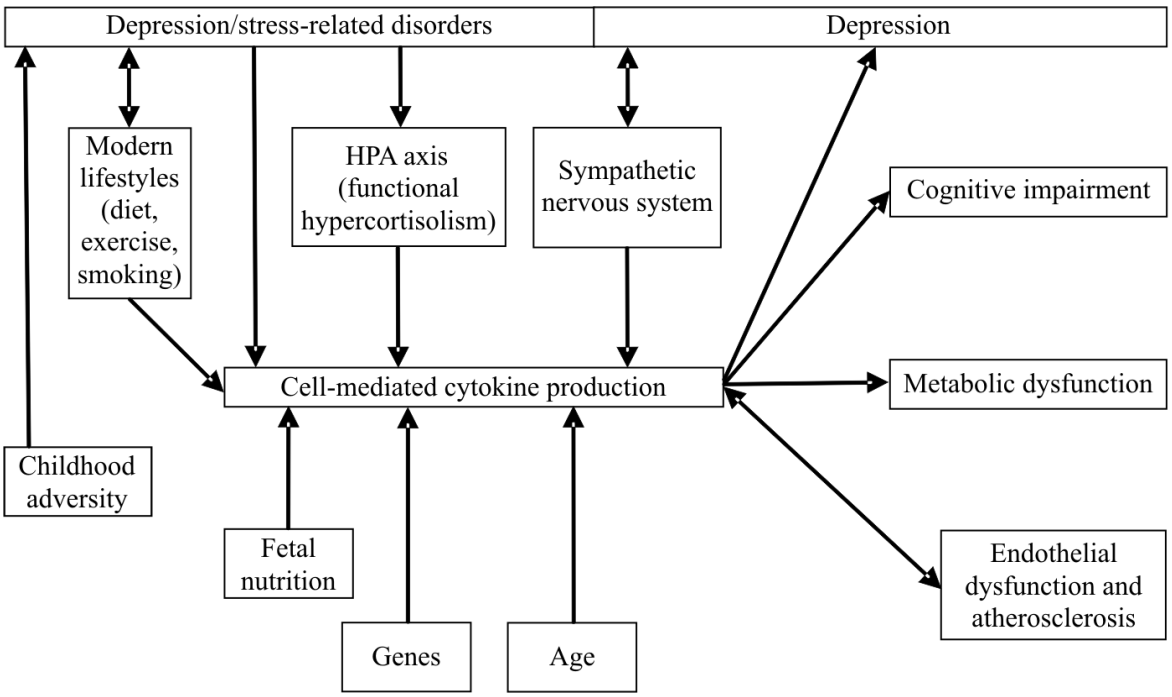

Figure 1 – ***Multifactorial model of depression (modified according to Ismail, 2010 [26]).***

Similar relationships had been noted between depression and the anterior cingulate cortex in the modulation of emotional behavior [27]. One of the neurotrophins responsible for neurogenesis here is the brain-derived neurotrophic factor (BDNF). Meta-analysis shows the level of BDNF in the serum of depressed subjects to be reduced threefold. Antidepressant treatment increases the blood level of BDNF. Although decreased serum BDNF is found in other mental disorders, such as schizophrenia, there is considerable interest about its relationship to depression and the action of antidepressants [28].

At a physiological level, the genetic perspective has been translated into the monoamine hypothesis of depression. This construct recognized that most antidepressant medications increase the level of one of more monoamine neurotransmitters – serotonin, noradrenaline and dopamine – in the synaptic cleft between cerebral neurons. Such medications may directly influence these neurotransmitter receptors. One contemporary account of the monoamine hypothesis proposes that a deficiency of certain neurotransmitters is responsible for the phenomenology of depression: thus, a decrease in noradrenaline may be associated with loss of alertness, attention, energy and interest in life. A reduction in serotonin to anxiety, obsessions and compulsions and a decrease in dopamine from the prefrontal cortex to loss of motivation, pleasure and reward [29]. Indeed, increased DA transporter levels and decreased DA levels were detected in patients with MDD [30, 31]. Higher levels of D2 receptor binding were identified in depressed patients in the right and left putamen, which correlated with motor retardation [32].

Depression has also been associated with immune mechanisms and the biological molecules involved in these processes termed cytokines [33]. In many ways, the phenomenology of depression is not unlike the illness experience when body is fighting an infection [34]. Elevated levels of circulating cytokines have been associated with depression and may explain some of the variations in depression seen in different tumors [35] (Figure 2).

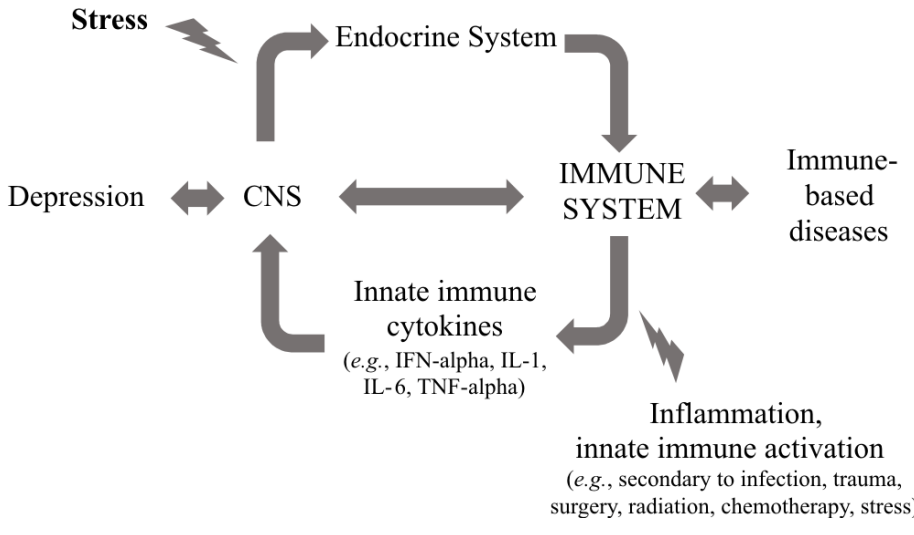

Figure 2 – ***Correlations between stress, neuroimmune function, inflammation and depression (Musselman et al., 2011 [33]).***

Another pathway to explain antidepressant mechanism of action that has received growing attention involves neuroplasticity. A marked cellular effect of several, but not all, antidepressant treatments is the induction of adult hippocampal neurogenesis – the process by which neural progenitors of the hippocampal subgranular zone divide mitotically to form new neurons that differentiate and integrate into the dentate gyrus [36]. The mechanisms by which neurons may restore mood are unknown, but activity-dependent increases in neurogenesis allow hippocampal networks to adapt and learn new experiences [37].

Role of neuroendocrine dysregulation

Many biological pathways are influenced by external stress. Failure to return to pre-stress activity appears to occur in several systems in depressed patients. Physical or psychological stress increases serum glucocorticoid concentrations. Small increases in serum glucocorticoid concentrations have been observed in depression and some depression-like symptoms can be produced in rodents by chronic administration of glucocorticoids [38].

Patients with Cushing's syndrome, who have extremely high concentrations of circulating cortisol also show depressive features and atrophic changes in the hippocampus. Nevertheless, this is not consistent for all types of depressive disorders since atypical depression, a subtype characterized by hyperphagia and hypersomnia also seems to be associated with hypercortisolemia [39].

Cytokines, which are humoral mediators of innate and adaptative immunity, are also important modulators of moood, explaining why, for example, 30% of individuals treated with recombinant interferons (proinflammatory cytokines) develop depression. Different types of neuropeptides have indeed a potential core role in the pathophysiology of MDD and are therefore being studied as possible treatment options (Table 1).

Table 1 – ***Neuropeptides with a potential role in MDD (adapted from Werner & Coveñas, 2010 [40])***

Neuropeptide	Possible treatment in MDD
CRH (corticotropin-releasing hormone)	Antagonists of the CRH-1 receptor exert an antidepressant effect and reduce the HPA axis dysfunction.
Thyrotropin-releasing hormone	In some patients with MDD, nocturnal thyrotropin releasing hormone administration produces a rapid antidepressant effect.
Cholecystokinin	Not studied.
Substance P	In clinical trials, the neurokinin-1 receptor antagonist showed no antidepressant effect.
Neuropeptide Y	Potential for neuropeptide Y analog or agonist to be of therapeutic value in MDD.
Galanin	A galanin receptor agonist has been described to exert an antidepressant effect.
Vasopressin	Not studied.
Opioids	Not studied.
Gastrin-releasing peptide	Not studied.
Angiotensin II	Not studied.
Orexin	Not studied.

Depression is a universal cross-cultural response to stressful events, particularly when the stress is chronic or the individual has no control over the situation. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to a powerful release of glucocorticoids into the blood stream [41]. Especially when depression is severe, it is also characterized by a constant overactivity of the HPA axis and a dysregulation of the autonomic nervous system (ANS) [42]. Additionally, it has to be considered that these systems interact with each other (Figure 3).

There is some preliminary evidence from several lines of research supporting sex differences in these pathways. It is known that gender-related biological factors influence glucocorticoid responses, which are important to downregulate cytokines. Therefore, the inflammatory process may be also mediated by these factors; *e.g.*, data indicate lower glucocorticoid sensitivity in women [43].

Results demonstrate that after a psychosocial stress test, free cortisol responses in men and women (in the luteal phase of the menstrual cycle) were similar, but large gender differences were observed with regard to glucocorticoid sensitivity. While in men glucocorticoid sensitivity was markedly increased one hour after stress, it was decreased in women, thus placing them at a higher risk for unchecked systemic inflammation. One prominent factor in affecting HPA functioning is sex steroids, with estrogen being a specific intriguing factor.

Sever studies have shown that postmenopausal women experience larger increases in cortisol secretion compared to men, in rest as well as in response to challenge, thus pointing to a general age-related increase of HPA reactivity [44]. This probably makes women more vulnerable for (recurrent) depression. Furthermore, depressed women show greater HPA axis dysregulation than depressed men as manifested by hypercortisolemia, which is different compared to the stress-response among non-depressed women [45]. While in male depressed patients and their matched controls the same plasma cortisol concentration was observed, female depressed patients showed significantly higher mean plasma cortisol concentration than their matched controls, as well as a significantly increased central drive of the HPA axis [46].

Another possible component in cytokine-related pathways may be sleep disturbances associated with depression [47]. The mechanisms that explain the associations among sleep disturbances and depression are not yet known, but recent data point as well to the role of inflammation, probably because lack of sleep can be also a source of stress [48]. Although the existing data predominantly refer to male samples, it can be assumed that this link in women might be even more strong, because women report more sleep disturbances than men, particularly menopausal and postmenopausal women [49]. As they seem to be especially vulnerable to the risks posed by inflammation, the higher levels of cytokines probably have more detrimental effects on their health.

Consistently, women's greater susceptibility to autoimmune diseases such as rheumatic arthritis, multiple sclerosis or myocarditis indicates significant gender differences in immune responses, with women showing a more vigorous cellular and humoral immune response and increased antibody production [50]. Therefore, it is not surprising that depression is also comorbid with these inflammatory disorders [51]. A salient area of research aiming at integrating depression, neuroendocrine, neuro-

immune and metabolic issues is the concept of allostatic load, referring to HPA axis functioning and to ANS, particularly the sympathetic response of the adrenal medulla and sympathetic nerves [52].

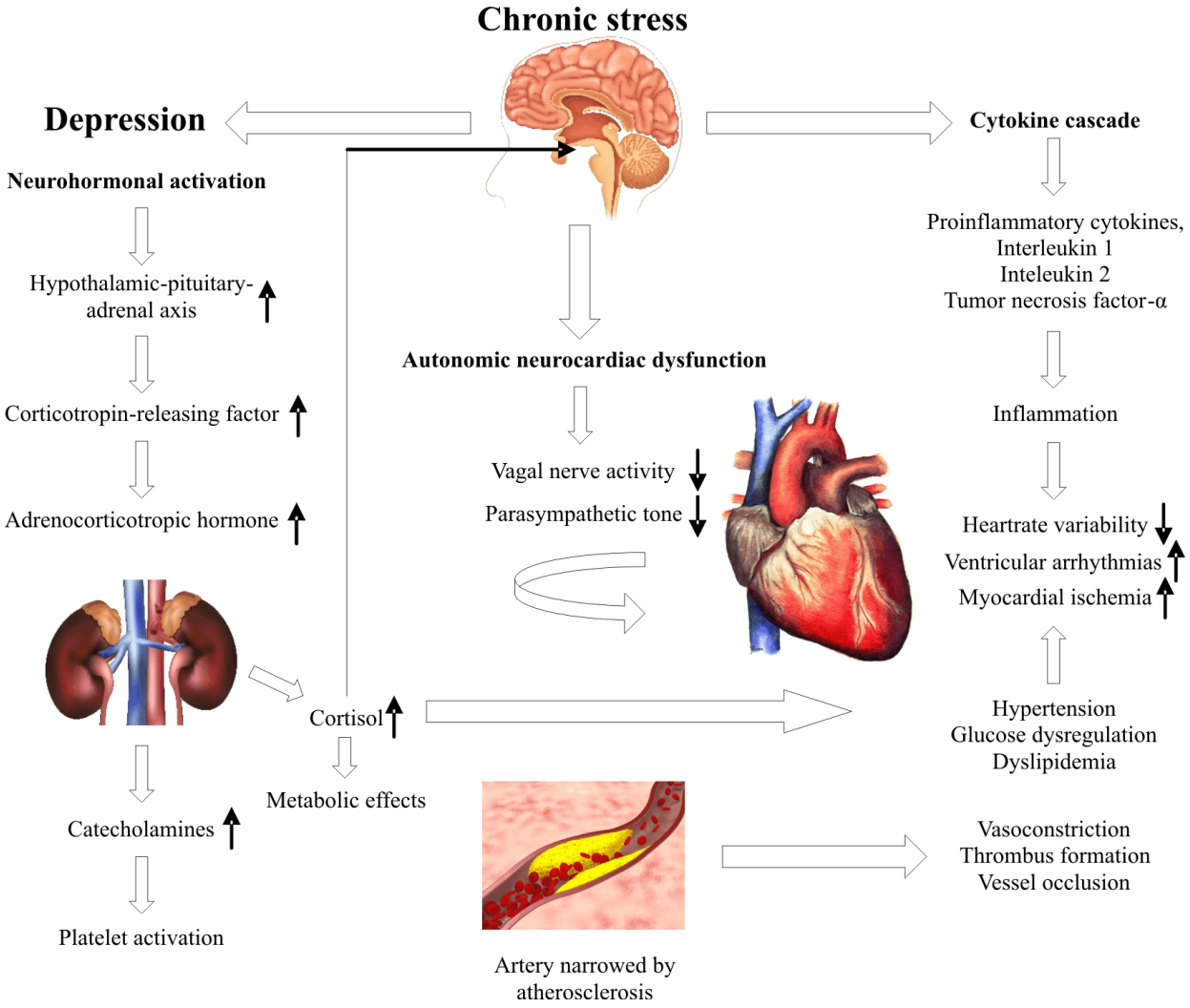

Figure 3 – ***The relationship between depression, endocrine system and cardiac function (according to Musselman et al., 1998 [53]).***

Assessing depressive-like symptoms and anxiety in rodent models

Modeling complex psychiatric disorders such as depression and anxiety in rodents is challenging. The majority of existing tests for depression may reflect depressive-like behaviors and anxiety-related states in the rodents but, although much has been learned about the underlying neuropathology in the human disorder, no abnormality has proven sufficiently robust or consistent enough to be used as a validation of rodent models [54, 55].

The most widely used test of depression, the forced swim test, is a simple and rapid test that had been used since the 1970s to screen compounds for antidepressant activity [56]. In the task, the rodents are subjected to a brief and acute period of stress and the time during which they respond in an active *versus* a passive way is recorded. In the forced swim-test, the rodent is placed in a water-filled cylinder from which it cannot escape and the immobility time is considered a measurement of "behavioral despair" [57]. Acute antidepressant treatment reduces the immobility time in this task and this has justified its use. However, the validity of this test may be questioned, firstly due to its major anthropomorphic leap defining immobility time as depression and secondly because effects have not been convincingly coupled to neuropathological changes [58].

Another major class of tests for depression-like behavior assessed anhedonia, one of the core symptoms of depression [59]. Most frequently examined is the rodents' interest in pleasurable activities such as intake of sucrose or engaging in social activity. One example, the sucrose consumption test is based on the preference for an intake of 1–2% sucrose solution over water, with decreased sucrose intake interpreted as depressive-like behavior [60].

The most common test of anxiety-related behavior in rodents is the elevated-plus maze, in which the relative time spent in the closed compared to the open arms can be considered a measure of anxiety [61]. The open-field test is another commonly used qualitative and quantitative measure of general locomotor activity and willingness to explore. Commonly the arena is marked in a grid and square-crossings, rearing and time spent moving are used to assess the activity of the rodent. By including

additional measures, such as time spent in the center of the field and activity during the first five minutes, the open-field test is also used as a test for anxiety [56].

Depressive-like behaviors have been demonstrated after both unilateral and bilateral 6-OHDA (6-hydroxydopamine) lesions, although loss of more specific functions influencing the neuropsychiatric findings was rarely examined. A study from 2008 was one of the firsts to characterize emotional deficits after bilateral 6-OHDA injections into the dorsal striatum of rats, reporting decreased sucrose consumption, increased immobility time in the forced swim test and the reduced percentage of entries into the open arms in the elevated-plus maze [62]. In another study using a similar type of 6-OHDA lesion in rats, it was shown the evidence of increased immobility time in the forced-swim test but, in contrast to the former study, decreased anxiety-like behavior and no changes in the preference for sucrose [63].

Bilateral nigral injections of 6-OHDA in rats also resulted, in the forced-swim test, in increased immobility time, which was strongly correlated with hippocampal reduction in levels of dopamine, serotonin and noradrenaline [64]. Surprisingly, considering the potential contralateral compensation, depressive-like behavior has also been reported after unilateral 6-OHDA lesions of the medial forebrain bundle [65].

Depressive and anxiety-related symptoms have also been demonstrated in mice with acute MPTP (1-methy-4-phenyl-1,2,3,6-tetrahydropyridine) lesions (20 mg/kg in four injections two hours apart) but, as with motor impairment data for this dose regime protocol, these neuropsychiatric findings have been inconsistent between studies [66, 67]. Other study demonstrated increased immobility in the tail-suspension test (version of the forced-swim test) and acute injections of L-DOPA as well a D2 agonist ameliorated this increase in immobility time [68, 69]. In contrast, two other studies using the same dosing regimen of MPTP did not see any depressive-like behavior assessed in terms of motivational change as decreased sucrose consumption [70, 71].

Several papers also demonstrated increased anxiety in rats after intranigral MPTP injection, assessed as less time in the open arms compared to controls in the elevated-plus maze [72, 73, 74]. Bilateral infusion of rotenone into the *substantia nigra pars compacta* of rats resulted in depressive-like behavior in the forced-swim test and decreased sucrose preference accompanied by reductions in serotonin levels in the hippocampus. Again, loss of more fine motor function was never accounted for as a confounding factor in the forced-swim test [64]. A recent work also highlighted that, after treatment with dexamethasone intraperitoneally administrated in saline solution equivalent to 0.2 mg/kg/day, hippocampus was the most intensely affected, being observed intense pinocytosis and vacuolization [75].

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

All authors have contributed equally to the manuscript.

Acknowledgments

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