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Review

Studies of Depression-Related States in Animal Models of Parkinsonism

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Abstract. The diagnosis of Parkinson's disease (PD) is solely based on movement disorders, but several non-motor deficits are common in PD. Depression often precedes the movement dysfunctions and continues to be a major concern during all stages of the disease. The pathophysiology of parkinsonian depression is largely unknown, but appears to partly differ from depression in patients without PD. Because of the increased awareness of the negative impact of depression on the quality of life of PD patients, there is a growing interest in developing animal models of parkinsonism that also recapitulate the depressive-like symptomatology. This review introduces paradigms for measurement of depression-like behaviors in rodents and summarizes data on behavioral, neurochemical and pharmacological changes in experimental PD models with relevance for depression-related states.

Keywords: Parkinson's disease, anhedonia, dopamine, serotonin, neurogenesis

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder next to Alzheimer's disease; with an annual incidence ranging from 110 to 330 cases per 100,000 individuals over the age 50 [1]. The diagnostic symptoms of PD are bradykinesia, accompanied by at least one of the three additional symptoms: rigidity, rest tremor and/or disturbance of postural reflexes. These motor symptoms are primarily due to the loss of dopaminergic neurons that project from the substantia nigra pars compacta (SNc) to the striatum and are treated with pharmacological agents which stimulate dopamine (DA) transmission. Most animal models of PD have employed toxins or genetic manipulations to recapitulate the motor symptomatology [2, 3]. However, it has long been recognised that the neuropathology underlying PD involves many brain areas beyond the dopaminergic nigrostriatal system, including areas that are not directly involved in motor control. These areas include the mesolimbic dopaminergic system, noradrenergic neurons in locus coeruleus, serotonergic neurons in the raphe nuclei, cholinergic neurons in the nucleus Basalis of Meynert, the dorsal vagal nucleus, the olfactory tubercle and large parts of the limbic cortex and neocortex [4]. Changes in the abovementioned systems may underlie many of the non-motor symptoms associated with PD.

Depression is the most frequent psychiatric complication in PD patients and one of the most important factors that reduce quality of life in PD [5]. Currently in Europe, there are approximately 1,000,000 patients with PD and between 36–53% of these patients also suffer from depression [5]. It has been argued that depression in PD is merely reactive to disability and loss of independent function, but about 20% of patients diagnosed with PD suffer from ongoing depression [6]; this may indicate that depression is part of the disease process rather than a result of diagnosis or living with PD. Studies have shown that people with PD have

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higher levels of depression than people with similar levels of disability from other causes (e.g. paraparesis), indicating that depression may be a part of PD itself [7]. It should be noted that it is difficult to diagnose depression in patients with PD because of the overlapping symptoms of the two disorders. Indeed, sleep disturbances, cognitive impairments, such as difficulties with concentration, and fatigue are also observed in non-depressed patients with PD, whereas typical symptoms of depression, like psychomotor retardation, bradykinesia and reduced mimic movements may also represent neurological deficits caused by PD. The high incidence of non-motor symptoms in PD, particularly depression, emphasizes the importance of studies of non-motor symptomatology in animal models to improve our understanding of pathophysiological mechanisms and possible treatments.

Here, we will introduce behavioral tests designed to assess depressive-like phenotypes in rodents and summarize data obtained with these tests in animal models of PD. The role of neurotransmitters, neurotrophic factors, steroids, neurogenesis and inflammation in depression and PD will then be briefly discussed (see summary in Fig. 1).

ANIMAL TESTS AND MODELS FOR DEPRESSION-LIKE SYMPTOMS

It should be acknowledged that it is very difficult to recapitulate behaviors of depression in rodents. There are, however, tests that can evaluate the potential presence of depression-related states. The most widely used tests, such as forced swim (FST) or tail suspension test (TST), were originally developed to detect behavioural responses to pharmacological antidepressant treatments. These tests have predictive validity for monoaminergic antidepressants. On the other hand, other experimental protocols such as chronic mild unpredictable stress (CUS) or social defeat are considered better animal models because they do not only have predictive validity, but also important aspects of face and construct validities. One important confounder, which needs to be kept in mind when studying a depressive-like state in PD models, is that most of the paradigms have a motor component. It is therefore critical to perform both the depression-related test and a pure motor test, for example in a locomotor box, under the same treatment conditions. However, in many instances more sensitive tests are needed to clearly elucidate motor skills in rodents. For example, depressive-like tests and models could be coupled with analyses of motor performances in the pole test, beam traversal test, skilled limb use and stepping test [for protocols see 8–10]. Another important aspect in depression-related tests and models is that they often involve a component of anxiety. In humans, these two disorders are often comorbid, although the underlying neuronal circuitries are thought to be partially distinct [11].

Several paradigms are used in the field of experimental depression research, but, as indicated below and in Table 1, only few of them have been applied to PD models.

Forced swim test

Porsolt and collaborators described in 1977 “a new behavioural method for inducing a depressed state”, which is, despite some weaknesses, still the most widely used animal test in depression research [12]. The paradigm is based on placing rodents, mice or rats, in a cylinder filled with water from which they

Table 1
Summary of different PD models in which a particular depression-like test has been used. Abbreviations: FST: forced swim test, TST: tail suspension test, LH: learned helplessness, NIH: novelty-induced hypophagia, NSF: novelty-suppressed feeding; ICSS: intracranial self-stimulation, CUS: chronic unpredictable stress, OB: Olfactory bulbectomy. ND: Not done

	6-OHDA	MPTP	rotenone	LPS	Reserpine	Parkin deficient	VMAT-2 deficient	VMAT-2 HET
FST	+ [31, 33, 34, 36]	+ [36]	+ [36]	− [36] + [214, 215]	+ [52]	− [63]	+/− [67]	+ [69]
TST	ND	+ [43] − [44]	ND	+ [215]	ND	− [63]	+/− [67]	+ [69]
LH	+ [37]	ND	ND	ND	ND	ND	ND	+ [69]
NIH/NSF	ND	ND	ND	ND	ND	ND	ND	− [69]
Sucrose preference	+ [31, 36] − [33]	+ [36] − [44]	+ [36]	− [36]	+ [51]	ND	ND	+ [69]
ICSS	ND	ND	ND	+/− [216]	ND	ND	ND	ND
CUS	ND	ND	ND	ND	ND	ND	ND	ND
Social defeat	ND	ND	ND	ND	ND	ND	ND	ND
OB	ND	ND	ND	+ [217]	ND	ND	ND	ND

cannot escape. Different types of behavior can then be measured: immobility as an indication of "behavioural despair", swimming and climbing [13]. Acute antidepressants can significantly reduce the time spent immobile [14]. Interestingly, drugs acting on different neurotransmitters systems seem to affect different active behaviours. Swimming is sensitive to serotonergic compounds, such as the selective serotonin reuptake inhibitors (SSRIs) and serotonin receptor agonists, while climbing is more affected by tricyclic antidepressants (TCAs) and noradrenergic compounds [15].

Tail suspension test

The TST is another test of "behavioural despair", but restricted to mice. The TST set-up consists of a horizontal bar where mice are suspended by tape at the tip of their tails [16]. In the TST, as in the FST, immobility is measured and significantly counteracted by acute antidepressant treatments [17]. However, recent studies showed that drugs tested in the TST for antidepressant properties showed strain-dependent effects. For example, the baseline and imipramine-induced behaviors of 11 different strains of mice showed clear inter-strain differences for both baseline scores and response to imipramine. In fact, a reduced immobility, i.e. positive antidepressant-like effect, of imipramine was only found in three strains (DBA/2J, NMRI and FVB/NJ) [18]. TST and FST were developed to detect antidepressant responses to monoaminergic antidepressants, but may disregard antidepressant potential of non-monoaminergic compounds. Moreover, in these tests an acute stressor is applied to normal animals while human depression involves long-lasting complex interactions between genetic and environmental factors. Furthermore, in the TST and FST a positive outcome is found already after a single administration of an antidepressant, while there is a considerable time (weeks-months) lag of response to the same antidepressant treatment in depressed patients. These limitations reduce the relevance of TST and FST.

Novelty-suppressed feeding (NSF) and Novelty-induced hypophagia (NIH)

The conflict between an anxious situation and an inherent need to feed is measured in the NSF test. The latency to eat a pellet in the center of a brightly lit novel cage by a food-deprived rodent is measured. As a control for hunger, the amount of pellet consumption is subsequently measured in the home cage. In this test, hyponeophagia, i.e. inhibition of feeding produced by exposure to novelty, is an assessment of the anxiety-related component of depression [19]. To avoid the food deprivation, a modified paradigm called NIH has been introduced. Although this test has been developed for mice, it may be adapted for use with other species. In the NIH test, animals are trained to drink sweetened condensed milk for three consecutive days in their home cage. The latency to drink, and the volume consumed are then recorded every 5 min for 30 min in the home cage during the 4th day and in a novel cage during the following day [20]. Interestingly, both these tests are sensitive to chronic, but not acute, antidepressant treatments [19].

Sucrose preference

This test is used as a measurement of anhedonia, which has been described as "markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day", considered as one of the core symptoms of depression [21]. The test measures the preference for, and consumption of, 1–2% sucrose solution over water in a two bottle choice setting. Anhedonic-like rodents show decreased preference for the sucrose solution, probably due to a reduced sense of reward of the sweet taste [22]. This test, practically easy to perform, is of particular importance in the characterization of the depressive-like phenotype of a PD model. Unlike many other tests, sucrose preference does not have a motor component as a possible confounder since it measures the percentage of sucrose consumption. Moreover, it has important face validity since anhedonia is a core symptom of depression not least in PD patients.

Intracranial self-stimulation (ICSS)

Another measure of the hedonic drive and its relation to the reward pathways is ICSS. Since brain regions, such as nucleus accumbens, hippocampus and amygdala, implicated in the human depression are also involved in the rodents' response to ICSS, this test could be relevant to study depressive-like behaviors [23]. The experimental procedure involves the surgical implantation of electrodes into one of the abovementioned brain regions of rats or mice. Animals are then trained to perform an active action to obtain rewarding electrical stimulations. The number of actions measures the sensitivity of the reward system and goal-oriented motivation [24]. In the ICSS paradigm, the stimulation does not induce any tolerance so measurements can be obtained over long periods of time [23].

Learned helplessness (LH)

In the LH model, mice or rats undergo an exposure phase during which they receive repeated unpredictable electric shocks (or other stressors) from which they cannot escape. On the day of test, when the animals have the possibility to escape after the shock, many of them choose not to do so. The escape deficit has been found to be reversible by both acute and chronic antidepressant treatments. The major criticisms of this test is that only a small percentage of exposed animals develop an escape deficit and that there are some strains of mice with an escape deficiency independent to stress exposure [25]. Since an active motor response is required from the tested animals, it is of particular importance to, in parallel, properly study the locomotor performance.

Chronic unpredictable stress

Much work in animal models follows the notion that experiences of stressful events, especially if repeated and unpredictable, are potent risk factors for developing depression. CUS involves exposing rodents to a series of repeated stressors (including swimming, strong light, cold, restrain, shocks) over several weeks [26]. After these stressors, animals develop a depression- and anhedonia-like phenotype, measured by for example sucrose preference reduction, that can be reversed by chronic, but not acute, antidepressant treatments.

Social defeat

In the social defeat model, the stress of the studied rodent is caused by the daily fighting with a physically superior and novel aggressor rodent. After some days, the defeated rodent develops common depression-like symptoms including anhedonia and social avoidance [27], which can be reversed by chronic, but not acute, antidepressant treatments [28].

Olfactory bulbectomy (OB)

The surgical removal of olfactory bulbs has been shown to induce increased locomotor activity and an avoidance-learning deficit in rodents that can be reversed by chronic antidepressants [29]. These symptoms seem to be caused by dysfunction of the hippocampal-amygdala pathway.

STUDIES OF THE DEPRESSION-LIKE PHENOTYPE IN ANIMAL MODELS OF PARKINSONISM

Classic neurotoxins-based models

6-hydroxydopamine (6-OHDA)

The neurotoxin 6-OHDA has played a fundamental role in preclinical research on PD [30]. Neurotoxic effects of 6-OHDA occur through a two-step mechanism involving accumulation of the toxin into catecholaminergic neurons, followed by alteration of cellular homeostasis and neuronal damage. Different 6-OHDA-based rodent models in which the toxin is variably injected into the nigrostriatal pathway (i.e. SNc, median forebrain bundle and striatum) have been developed throughout the years. These models result in moderate to complete nigrostriatal neurodegeneration, thus providing appropriate paradigms for modeling of distinct parameters, from molecular markers to fine motor symptoms of PD. Only recently, this model has been used to study depression-like behaviors in PD and reported results are different depending on the chosen lesion paradigm. Bilateral 6-OHDA infusion in the striatum caused a fast damage of the dopaminergic terminals with about 59% of striatal DA loss, followed by retrograde loss of tyrosine hydroxylase (TH)-positive cells in the SNc [31]. Under these circumstances, the SNc cell loss takes place gradually over several weeks [32]. This progression in nigral degeneration creates a time window that can be used for the investigation of pre-motor symptoms of PD. In this model, reduced sucrose consumption and increased immobility in the FST were found, despite that the locomotor activity was not impaired. However, no sensitive fine movement tests were performed in this study to properly assess motor deficits. Another study also found that a mild bilateral striatal lesion (36% striatal DA loss) caused increased immobility in the FST, but in this case without any effect on sucrose consumption [33]. In this study [33] the alteration in the FST was found 6 weeks after the intrastriatal 6-OHDA lesion, whereas a motor impairment in the locomotor activity was found after 9 weeks. In this 6-OHDA paradigm, emergence of impairments seems to follow a temporal profile similar to that occurring in PD patients. Recently, the contribution of a severe 6-OHDA lesion (>95% DA loss in striatal tissue) on FST was studied by using a unilateral medial forebrain bundle lesion model [34, 35] and evidence of a depression-like behavioral profile was observed. However, the severity of the lesion resulted in significant motor disability, which makes

extrapolations to affective processes difficult. In general, unilateral models are difficult to interpret because the responses of the animals can result from a contralateral compensation or a bias towards movements in one direction. By bilaterally injecting the neurotoxin directly into the SNc and achieving a 50% nigral neuronal loss without affecting other areas, it has been shown that rats develop both anhedonia, measured by sucrose consumption, and behavioral despair in the FST [36]. Likewise, unilateral 6-OHDA lesion of the SNc resulted in depressive-like behaviors using the LH model in rats [37]. These authors found similar results when injecting 6-OHDA unilaterally into the ventral tegmental area (VTA) suggesting an involvement of the mesolimbic DA pathway in depression.

1-methyl-4-phenyl-tetrahydropiridine (MPTP)

The incidence of PD is known to be associated with exposure to a wide range of environmental, industrial and agrochemical toxins as well as accidentally produced narcotics. Ingestion or administration of some of those agents to rodents can induce neurodegeneration with rather selective vulnerability of ventral mesencephalic DA neurons accompanied by behavioral deficits. Among these agents, MPTP has received most attention as an experimental tool for modeling PD. The propensity of MPTP to cause a parkinsonian syndrome was discovered in drug addicts who mistakenly self-administered the compound after a poorly conducted chemical synthesis of a designer drug of abuse [38]. The compound is widely used in mice and non-human primates while it has a limited toxicity in rats due to differences in the ability to convert MPTP to MPP+ ion, the active form of the toxin. Several different protocols are used with different outcomes in terms of motor impairments. The acute protocol, usually based on 4 intraperitoneal injections of 20 mg/kg of MPTP given 2 hours apart, has resulted in inconsistent data in motor impairments [39–42]. To try to find a more reliable test than locomotion to study motor impairment in this model, Mori and collaborators used the TST and found increased immobility time, but preserved locomotion, in toxin-treated mice [43]. The increased immobility in the TST was counteracted by dopaminergic stimulants, such D_2 receptor agonists and L-DOPA. D_2 receptor agonists, but less so L-DOPA, have antidepressant properties (see below), indicating that the found immobility under baseline conditions may represent motor dysfunction rather than a depression-like phenotype. In this context, it is important to keep in mind that the TST is not a valid test of motor function. One study using the same MPTP treatment paradigm in mice reported no depressive-like behaviors in the TST and sucrose consumption tests [44]. In contrast, rats intracranially injected with MPTP in the SNc showed both anhedonia and behavioral despair [36]. The conflicting data of the abovementioned studies probably relates to different neurotoxin lesioning paradigms, time after lesion and species used. In contrast to the acute model, the chronic paradigm of MPTP administration, such as twice per week for 5 weeks, seems to provide more reproducible results on tests of motor impairment [10, 45]. At the moment, no studies have been done to characterize the depressive-like behaviors in the chronic MPTP model.

Other drug-induced models

Rotenone

Rotenone is a pesticide that has attracted particular attention because it can, like MPTP, damage mitochondrial complex I in a pattern similar to what found in PD. However, several studies have pointed out the non-specific toxicity of rotenone paradigms suggesting the need of a careful use of this model and critical understanding of the outcomes when relating to parkinsonism [46, 47]. Bilaterally injected-toxin into the SNc was able to produce depressive-like behaviors assessed through the FST and the sucrose preference test in rats, although the involvement of a motor impairment may have confounded the FST results [36]. In this study, bilateral intranigral administration of LPS was also used to study FST. LPS stimulates neuroinflammatory processes and, under some circumstances, potentiates neurodegeneration and, as discussed below, there is evidence of a low-grade, but persistent, neuroinflammation in PD. However, intranigral LPS caused no significant behavioral alterations.

Reserpine

An old model of parkinsonism in rodents and rabbits is treatment with reserpine, which interferes with the storage of catecholamines in intracellular granules, resulting in monoamine depletion in nerve terminals and in the induction of hypolocomotion and muscular rigidity [48, 49]. Using reserpinized animals, it was shown that L-DOPA is the precursor of DA and has strong stimulatory locomotor properties [50]. Reserpinezed mice displayed a significant decrease in sucrose preference compared to vehicle treated mice whereas there was no difference in the total liquid consumption [51]. Moreover, rats treated with reserpine showed an increased immobility time in the FST at a

dose that did not induce any locomotive impairment in the open-field test [52].

Genetic models

Most cases of PD are idiopathic with no evident genetic causality. However, familial PD has been identified and more than 11 loci and 16 genes have been reported [53]. The first familial PD mutation was in the α-synuclein gene [54]. Subsequent work identified α-synuclein as an abundant protein in the core of Lewy bodies [55], the globular protein inclusions in neurons considered the principal neuropathological hallmark of idiopathic PD. Later, mutations have been identified in several other genes, including leucine-rich repeat kinase 2 (LRRK2), Parkin, DJ-1, and PTEN-induced kinase 1 (PINK1). Although the incidence of familial PD is low, the identification of these genes and their protein products has provided important insight into the pathophysiology of PD. Several of these genes are associated with proteins components of the mitochondrial energy chain or implicated in protein folding and degradation via the ubiquitin-proteasome system [53].

Neurotoxin PD models reproduce the characteristic loss of dopaminergic neurons and result in motor impairments, but lack most of the other key characteristics of PD, such as the age-dependent progressive neuronal loss and the presence of Lewy bodies. Because of these limitations, major efforts have been made to generate new animal models of PD, particularly the creation of mutant mice expressing genetic alterations similar to those found in humans. α-synuclein overexpression has attracted particular attention and several genetically-modified transgenic lines have been made using different promoters [56]. Unfortunately, none of the models fully replicate the neurodegenerative pattern or behaviors of PD. However, interesting studies performed in mice carrying a chromosomal deletion of the α-synuclein locus showed that knock out (KO) animals have higher level of ICSS compared with control group. This effect can probably be attributed to a higher level of DA release in the mesolimbic terminals due to the larger vesicular capacity found in these mice [57]. An alternative procedure to overexpress α-synuclein is viral vector-mediated delivery to specific targets, such as the SNc. This strategy results in a model that more closely mirrors the PD pathology with neuronal inclusions [58]. So far, no studies have examined the depressive-like phenotype of this model. Several genetic lines carrying a deletion of different exons in the parkin gene have also been generated [59–62], but none of them showed a consistent phenotype, probably due to different genetic backgrounds. A mouse line lacking exon 2 of the parkin gene was investigated in terms of non-motor behaviors, but no significant phenotypes were found in the FST and TST [63].

The recent report of a transgenic animal model of PD that carries the LRRK2 mutation has also attracted considerable interest [64] and genetic mouse models have recently been developed with mutated PINK1 and DJ1. Overall, in these genetic lines based on familiar PD, significant behavioral impairments have been difficult to observe and limited efforts have been made to study non-motor features of PD.

Within the context of genetic mouse lines, Mooslehner and co-authors generated a line expressing 5% of the normal level of the vesicular monoamine transporter 2 (VMAT2), which regulates packaging of not only DA, but also noradrenalin (NA) and serotonin (5-HT) into synaptic vesicles in neurons [65]. This line was characterized as a potential model of PD and showed moderate, but progressive loss of nigrostriatal neurons and motor impairment [66]. VMAT2 deficiency resulted in significant depletion of NA and 5-HT levels, allowing broad investigations on the role of monoamines in the generation of non-motor symptoms in PD. The recent article by Taylor and co-authors demonstrates that, indeed, VMAT2-deficient mice exhibit an age-dependent phenotype mimicking many of the non-motor symptoms of PD [67]. Of particular relevance, VMAT2-deficient mice displayed a clear age-dependent depressive-like phenotype as only old (12–15 months), but not young (4–6 months), mice showed a significant increase in immobility time in the FST and TST [67]. Likewise, VMAT2-heterozygote (HET) mice, with a 42% DA deficiency in the striatum compared to WT [68], showed a depressive-like phenotype with increased immobility time in the TST and FST, decreased sucrose consumption and a robust increase in LH. However, no difference in the NSF test was found when comparing WT and VMAT2-HET mice, but this test has a high anxiety-like component [69].

NEURONAL CIRCUITRIES INVOLVED IN DEPRESSION AND PD

Basal ganglia are a group of interconnected nuclei (SNc, SN reticulata, striatum, globus pallidus, entopeduncular nucleus and subthalamic nucleus) that connect with different parts of the cerebral cortex and thalamus. The pathological changes in these areas in

relation to motor symptoms of PD have been extensively investigated [e.g. 70, 71]. However, some studies have also examined their role in non-motor functions [72]. Moreover, although PD is mainly known to be a disorder associated with the nigrostriatal DA cell loss, dysfunctions of additional neurotransmitter systems also participate in the symptomatology of PD, not least in non-motor symptoms. Interactions between 5-HT, NA and DA have been strongly implicated in reward-related behaviors and depression [73]. According to the Braak staging of PD pathology, NA and 5-HT dysfunctions occur prior to significant degradation of DA neurons [4, 74]. It is also well known that the activities of DA neurons in the SNc and of dopaminoceptive GABAergic neurons in the striatum are regulated by glutamate and modulated by acetylcholine and adenosine in the processing of proper movements [75, 76]. As discussed below, all these neurotransmitters may also play an important role in the pathophysiology of parkinsonian depression and represent targets for future treatments. It should also be emphasized that these neurotransmitters are abundant in several neuronal circuitries outside the basal ganglia, such as nucleus accumbens, hippocampus, amygdala and frontal cortex, which are implicated in depression and somewhat affected in PD.

ROLE OF NEUROTRANSMITTERS IN DEPRESSION AND PD – FOCUS ON DATA FROM ANIMAL STUDIES

Dopamine

DA has been extensively linked to the development and treatment of affective behaviors in the general population and in experimental models of depression [77, 78]. Clinical studies have established an association between decreased binding of the DA transporter in the ventral striatum and depressive symptoms in human [79].

The role of DA in depression has been extensively studied also in several animal models. For example, the effect of TCAs in rats was found to be related to the increased level of extracellular DA in the nucleus accumbens and prefrontal cortex after strong inhibition of the DA uptake [80]. Chronic antidepressants have been shown to produce sensitization of behavioral response to drugs acting on D_2/D_3 receptors in the nucleus accumbens [81]. Furthermore, anhedonic animals seem to respond with locomotor sensitization both to D_2/D_3 agonists and antidepressant drugs [82].

If diminished DA levels by themselves are leading to depression in PD, DA replacement therapy with L-DOPA should reduce depression. However, DA-depleted rats have been shown to express enhanced LH behavior, an effect that is only partially counteracted by L-DOPA [37]. In a recent study conducted in 6-OHDA lesioned rats, L-DOPA was shown to induce supraphysiological release of DA in prefrontal cortex and hippocampus [83]. The excessive efflux of DA in these areas could underlie the relatively low antidepressant efficacy of L-DOPA since it might cause agitation and psychosis. On the other hand, drugs such as the clinically used antidepressant bupropion, that inhibit DA reuptake, counteract the depressive-like behaviors of VMAT2-HET mice in the TST [69]. The effect of specific DA agonists has been also studied. Their different receptor specificity seems to possibly influence their effectiveness [84]. Whereas D_2 receptors in the nigrostriatal pathway are mainly involved in modulation of motor functions, D_3 receptors in the mesolimbic dopaminergic system appear to be more involved in the regulation of mood and behavior. The preferential stimulation of D_3 receptors may explain antidepressant and anti-anhedonic properties of DA agonists like ropinirole and pramipexole. In binding studies, pramipexole exerted the greatest D_3 versus D_2 preference compared to other currently available DA agonists used for the treatment of PD [85]. In various animal models, pramipexole have antidepressant [86, 87] and hedonic effects [82].

It is important to note that evaluation of antidepressant effects of dopaminomimetics in animal models of PD is extremely challenging. For example, hemiparkinsonian rodents treated with dopaminergic drugs show turning behavior that can disturb the performance in the depression-like test. Furthermore, administration of dopaminergic compounds such as L-DOPA, especially if given chronically, can cause dyskinetic movements and these repetitive and purposeless behaviors can also influence a good test execution.

Noradrenaline

Noradrenergic neurons are degenerated in the locus coeruleus of PD patients prior to nigral DA neurons degeneration [4]. Lower level of DA/NA transporter in the locus coeruleus seems to correlate with an increase of incidence for depression [79]. Accordingly, a recent positron emission tomography study in humans, showed that binding of [^{11}C]RTI-32 in brain regions that receive noradrenergic innervations was significantly lower in depressed patients with PD

when compared to non-depressed patients with PD [79]. NA levels have not been much studied in animal models of depression in PD and results are very contradictory. Increased level of NA was shown in the prefrontal cortex and hippocampus of 6-OHDA lesioned rats while no significant difference was found in rats intracranially injected with other neurotoxins, such as MPTP, rotenone or LPS [31, 36]. In the depressive-like VMAT2-deficent mice, a strong decrease of both DA and NA was observed in the striatum, cortex and hippocampus [67]. Furthermore, the increased immobility in the TST found in this model has been shown to be reduced in mice treated with the NA reuptake inhibitors, reboxetine or desipramine [67, 69].

Serotonin

The role of 5-HT in depression in PD is still not clear. In a recent study, neuronal loss and gliosis was observed in the SNc and locus coeruleus but not in the raphe nuclei of PD patients with depression [88]. In contrast, others studies have found increased pathology in the raphe nuclei of depressed compared to non-depressed PD patients [89, 90]. Moreover, levels of 5-hydroxyindoleaceticacid (5-HIAA, a 5-HT metabolite) have been shown to be lower in the cerebrospinal fluid of depressed PD patients in several [91, 92], but not all [93] studies.

In animals, lesion of dopaminergic system with 6-OHDA or MPTP causes changes in the 5-HT system. Interestingly, this effect depends on several factors like age, toxin used and protocol of lesion. Some studies showed no 5-HT system impairment after MPTP treatment [94] but others found a significant depletion of 5-HT following MPTP lesion in mouse [44, 95]. On the other hand, no correlation was found between the decrease in 5-HT with a depressive-like phenotype. In contrast, in a rat study where comparisons were made of several neurotoxins, the degree of lesioning of the 5-HT and DA systems correlated significantly with swimming or immobility in the FST [36]. A more detailed analysis revealed that neurotoxin-mediated reductions in DA correlated well with increased immobility, whereas neurotoxin-mediated lowering of 5-HT levels correlated better with a decrease in the swimming parameters [36]. Studies performed in the 6-OHDA model showed that imipramine could improve depression-like behavior in the FST [96]. It is noteworthy that L-DOPA has been shown to affect 5-HT and NA levels in several areas of the brain, such as prefrontal cortex, amygdala and hippocampus, and these effects have been seen in intact rats [97] as well as DA-depleted animals [98, 99]. L-DOPA treatment can indeed, via decarboxylation and beta-hydroxylation, form NA and, via decarboxylation in 5-HT neurons, form "false DA" that displaces and lowers 5-HT. An inhibition of the 5-HT system in "emotional" regions suggests that L-DOPA treatment might even promote the development of affective symptoms.

5-HT_{1A} receptors are important in the regulation of mood and emotionality and are thought to mediate some therapeutic actions of antidepressants including SSRIs [100]. SSRIs, TCAs, and electroconvulsive shock therapy increase post-synaptic 5-HT_{1A} receptor signaling through direct or indirect effects [100]. Sarizotan has high affinities to 5-HT_{1A} receptors and DA $D_4 > D_3 > D_2$ receptors, with the profile of a 5-HT_{1A} receptor agonist and D_2-like receptor partial agonist [101]. It was recently found that sarizotan significantly reduced the immobility in the FST of unilaterally 6-OHDA lesioned rats [35].

Amino acids – glutamate and GABA

Glutamate is the major excitatory neurotransmitter in the brain and acts via multiple metabotropic and ionotropic receptors. Recent findings indicate that levels of glutamate are reduced in the anterior cingulate cortex of depressed subjects [102, 103] while these levels are normalized upon successful antidepressant treatment [104]. Glutamate has a direct modulatory function of the 5-HT system [105] and vice-versa. Chronic, but not acute, treatment with a variety of monoamine-based antidepressants leads to an increase in the phosphorylation state of synaptic AMPA and a down-regulation of NMDA glutamate receptor levels [106]. In clinical trials, the glutamate NMDA receptor antagonist, ketamine, exerted a rapid and sustained antidepressant effect in formerly treatment resistant patients [107]. In pre-clinical studies, ketamine reduced the immobility time in the TST for 72 h [108]. Moreover, acute administration of ketamine decreased the number of escape failures in the LH paradigm in rats and this rapid response was related to the synthesis of the brain derived neurotrophic factor (BDNF) [109]. Since there are major dysfunctions in corticostriatal glutamatergic transmission in PD, it is possible that modulation of glutamatergic transmission may exert antidepressant properties also in PD patients. At the moment, no studies have examined antidepressant effects of glutamate compounds in PD models.

Another amino acid, GABA, is the predominant inhibitory neurotransmitter of the brain. Accumulating evidence over the past years indicate that also GABA transmission is critically altered in depression with changes in several different neuronal circuitries [110] and antidepressant treatments, such as SSRIs and TCAs, have effect on GABAergic neurotransmission [111]. Pre-clinical studies showed a depressive-like phenotype in mouse lines with deficit in the expression of different subtypes of the $GABA_A$ receptor, including HET mice for the gamma subunit [112, 113] and KO mice for the delta subunit [114]. So far, the role of GABA transmission in depression in PD has not been evaluated in human or animal models.

Acetylcholine

Manipulation of acetylcholine receptors play an important role in emotional states including depression [115]. Scopolamine, a muscarinic receptor antagonist, exhibits antidepressant properties in depressed patients [116] and animal data also suggest a role for muscarinic receptors in depression. For example, the Flinders Sensitive rat line of depression is bred for increased sensitivity of muscarinic receptors and exhibits increases in response to cholinomimetic drugs in the FST [117].

Effects of acetylcholine on mood also involve nicotine receptors [118]. In an animal model of depression, nicotine receptor antagonists, especially mecamylamine, showed antidepressant properties [119, 120], and this effect was lost in mice lacking $\alpha 7$ or $\beta 2$ receptor subunits [121]. Paradoxically, nicotinic receptor agonists, e.g. cytisine, sazetidine-A or varenicline, also showed antidepressant-like properties in mice [120, 122–124]. Similarly, acute and chronic nicotine reduced immobility time in the FST in the Flinders Sensitive Line of rats [125].

Anticholinergic agents have been used for many years in the treatment of PD and are especially beneficial against parkinsonian tremor [126]. Interestingly, a recent clinical finding provided evidences for the role of cholinergic neurotransmission in parkinsonian depression showing that reduced $\alpha 4\beta 2$*-nAChR binding in patients with PD within subcortical and cortical regions was associated with the severity of depressive symptoms [127].

Adenosine

Adenosine has an important modulatory role in the central nervous system. Low concentration of adenosine is physiologically present in the extracellular fluid while it increases exponentially under pathological conditions [128]. Among the four distinct receptors (A_1, A_{2A}, A_{2B}, and A_3), A_1 receptors are widely abundant in the brain, especially in the cortex, while A_{2A} receptors are located mainly in the striatum [128, 129]. The strong anatomical and functional interaction between A_{2A} and D_2 receptors in the indirect striatopallidal GABAergic pathway [130] led to the important finding that A_{2A} receptors antagonists can significantly improve motor dysfunctions in PD [131–133]. Subsequently, antagonism of A_{2A} receptors has also been shown to have neuroprotective effect in the MPTP and 6-OHDA models of PD [134, 135].

Interestingly, modulation of the adenosine system tends to produce depressant-like effects in animal models. Stimulation of adenosine receptors induces a state of LH similar to that observed in animal models of depression [136, 137] and increases the immobility time in the FST with antidepressants reversing this effect [138]. Moreover, adenosine A_{2A} antagonists have antidepressant like properties in several animal paradigms [139, 140].

ROLE OF STEROIDS IN DEPRESSION AND PD

Stress is a common environmental trigger of depression and a crucial component in human depression is a dysfunctional HPA (hypothalamic-pituitary-adrenal) axis [141, 142]. In major depressive disorder, an excessive activation of this circuit has been found in almost 50% of depressed individuals [143, 144]. Depressed patients, as well as patients with Cushing's disease, have reduced hippocampal volume [141, 142]. Corticosteroids may cause this effect via several mechanisms including reduced neurogenesis and shrinkage of the dendritic tree of hippocampal neurons [142]. In line with these findings, glucocorticoid and corticotropin-releasing factor receptor antagonists are currently being tested as antidepressants in clinical trials. However, it should be emphasized that atypical forms of depression, such as "burnout", are accompanied by hypocortisolemia [141, 142]. It is likely that changes in the HPA axis are involved in parkinsonian depression, but it remains largely neglected both in patient and animal studies.

Depression and depression-related diseases are more common in females than males, both in a normal population and among PD patients, suggesting an important involvement of gonadal steroids [145]. Since particular depressive states, such as post partum

depression, seem to follow body concentration of progesterone and estrogen that dramatically drops after the delivery, several models of hormonal withdrawal have been developed in animals and all of them have been associated with depressive-like behaviors [146, 147]. Interestingly, progesterone has been showed to prevent depressive-like FST behavior in parkinsonian animals [96].

Neurosteroids are synthesized or metabolized in the brain and can affect neuronal functions. Decreased levels of pregnenolone, the most abundant steroid in the CNS, were found in depressed individuals [148]. Moreover, the administration of this steroid to rodents was able to decrease the immobility time in the FST [149]. The importance of pregnenolone for effects of antidepressant drugs was suggested when increased levels were found in the cerebral cortex and hippocampus of imipramine-treated rats [150, 151]. A similar compound, allopregnenolone, was also shown to have a link with depression in human and animal studies [152, 153]. At the moment, there are no studies on the role of neurosteroids in parkinsonian depression.

ROLE OF NEUROTROPHIC FACTORS IN DEPRESSION AND PD

Brain-derived neurotrophic factor

BDNF is the most abundant neurotrophin expressed in the brain [154]. It promotes neuronal survival and differentiation and modulates synaptic plasticity through the receptor tyrosine kinase (Trk) B [155].

Post mortem studies showed that BDNF levels are reduced in the SNc of parkinsonian brain [156–158] and this decrease seems to be a result of reduced transcription of the BDNF gene. It has also been demonstrated that pathogenic mutations of α-synuclein, associated with early-onset familiar PD are linked to decreased BDNF production [159].

Moreover, several animal studies evaluated the link between decreased BDNF and PD. The infusion of antisense BDNF oligonucleotides into rat SNc generated animals that exhibit some characteristics of the classical models of PD [160]. Animals completely lacking BDNF in the midbrain and in the hindbrain displayed a persistent reduction of DA in the SNc [161]. Moreover, mice expressing only half of the normal levels of BDNF were shown to have a compromised striatal DA output and impaired behavioral response [162]. Recently, TrkB hypomorphic mutants showed late-onset DA neuronal loss that is confined in the SNc and does not appear until 12 months of age [163].

Accordingly, the delivery of BDNF in experimental animal models of PD rescued degenerating DA neurons in the SNc [164]. Intrastriatal grafts of fibroblasts, genetically modified to produce BDNF, were used to prevent the 6-OHDA-induced loss of neurons in rats [165] while cell-mediated delivery of BDNF increased DA levels in the MPTP model of PD [166]. Furthermore, nigral infusion of BDNF in mice partially reversed MPTP-induced DA decrease.

There are clear links between BDNF and depression. In fact, depressed patients showed a reduction in hippocampal [167] and serum BDNF level [168] and several antidepressant drugs, given chronically, cause a normalization. There is also evidence that BDNF can regulate functions relevant to antidepressant-response in rats. Chronic infusion of BDNF into posterior midbrain nuclei resulted in effects that are similar to those of antidepressants in FST and LH [169]. Furthermore, administration of BDNF directly into localized regions of the hippocampus similarly resulted in antidepressant properties in these behavioral models [170]. No studies on the role of BDNF in depressive behaviors have been performed in PD models.

Vascular endothelial growth factor (VEGF)

VEGF plays an important role in depression and in mediating the effect of common antidepressant treatments. Intracranial infusion of VEGF in animals showed antidepressant properties in depression-like paradigms, such LH, FST and NSF [171]. Interestingly, infusion of the VEGF inhibitor, SU5416, blocked the behavioral effect of desipramine and fluoxetine [171, 172].

Moreover, VEGF has also been studied for its beneficial effect on neurons and reduced level of VEGF can induce neurodegeneration by impairing vasoregulation, neural tissue perfusion, and normal functioning of perivascular autonomic nerves. VEGF gene transfer, mediated by adeno-associated virus, has been shown to promote dopaminergic neuronal survival in 6-OHDA lesioned rats [173]. VEGF levels are increased upon L-DOPA treatment in PD models [174]. It would therefore be interesting to study whether VEGF could exert also antidepressant properties in PD models.

ADULT NEUROGENESIS IN DEPRESSION AND PD

Newborn neurons are produced in the adult brain in rodents as well as humans [175]. Although neurogenesis in adult is much less frequent than in

embryonic development, several thousand new granule neurons are generated every day [176]. Neurogenesis occurs in two different areas of the brain: the neurons that are born in the subventricular zone (SVZ) of the lateral ventricle migrate into the olfactory bulb (OB) and become interneurons while the neurons born in the subgranular zone (SGZ) of the dentate gyrus (DG) migrate to the granular layer of the DG to eventually become mature granule neurons.

Early studies showed that various antidepressant regimens to rodents increase cell proliferation and neurogenesis in the SGZ [141] and a "neurogenic theory" postulated a link between decreased rate of neurogenesis in the SGZ with the vulnerability for depression. However, more recent work has shown that attenuated neurogenesis per se is not enough to carry a depression-like phenotype. When studying neurogenesis in rodents, the strain is of critical importance due to varying levels of proliferation and neurogenic response between strains as well as response to stress [177–179].

Interestingly, alterations in neurogenesis have also been observed in PD. The number of proliferating cells in the SVZ of the striatum and in the SGZ of the DG were reported to be reduced in post-mortem brains of individuals with PD and restored by treatment with L-DOPA or selective agonists for D_2 receptors [178]. Decreased cell proliferation was also found in several experimental PD models, such as 6-OHDA-lesioned rats, MPTP-injected mice and monkeys and in the transgenic mouse model expressing human α-synuclein [178, 180–182]. An altered neurogenesis has also been observed in various-synuclein overexpressing models of PD with reduced proliferation in both the DG [182–184] and SVZ/OB systems [185]. However, recent studies showed that the proliferative capacity in the SVZ of MPTP-treated animals and aphakia mice is not affected while mice with depletion of dopaminergic neurons in the ventrolateral VTA have impaired SVZ proliferation [186, 187]. Two frequently used DA agonists (ropinirole and pramipexole) showed a regenerative effect on SVZ proliferation in PD models [178, 188]. Likewise, sarizotan also increased cell proliferation in the SVZ and SGZ especially in the 6-OHDA-lesioned hemisphere [35] and, as mentioned above, sarizotan has affinity for serotonin 5-HT_{1A} receptors that are known to regulate neurogenesis in the SGZ. Indeed, 5-HT_{1A} receptor KO mice have been shown to be insensitive to the neurogenic effects of fluoxetine in the SGZ [189]. In accordance, selective antagonism at 5-HT_{1A} receptors decreased cell proliferation in the SGZ [190] and, vice versa, stimulation of 5-HT_{1A} receptors increased cell proliferation in this region [191].

INFLAMMATION IN DEPRESSION AND PD

In both patients and experimental models of PD, neuroinflammation appears to be an ubiquitous finding together with phagocyte activation, increased synthesis and release of proinflammatory cytokines and complement activation. In particular, activation of microglial cells has been found in several paradigms of PD such as the MPTP [10], rotenone [192] and 6-OHDA [193] models. LPS-induced microglial activation seems to induce neurodegeneration of DA neurons in the SNc [194–196]. More recent studies clearly indicate that inflammatory cytokines as TNF-α or IL-6 are toxic to neurons [197, 198]. Furthermore, genetic inactivation of COX-2 or TNF-α receptors has been shown to protect DA neurons against MPTP-induced neurotoxicity [198, 199]. Likewise non-steroidal anti-inflammatory drugs have been shown to be potential agents against neurodegeneration in animal models of PD [200, 201]. Moreover, minocycline, that decreases the production of several pro-inflammatory molecules, was shown to have neuroprotective effect on DA neurons in MPTP, LPS and 6-OHDA animal models of PD [202–205].

Interestingly, various clinical and pre-clinical findings suggest that depression is associated with an increased production of pro-inflammatory cytokines [206–210]. Cytokine administration or systemic administration of LPS induced depression-like symptoms in animal models of depression [211–213]. Indeed, recent studies showed that systemic LPS administration increased immobility in both FST and TST in mice [214, 215]. Furthermore, the effect of acute and repeated administration of LPS was studied in the ICSS paradigm. Compared to vehicle-treated animals, acute exposure to LPS induced a dramatic loss of ICSS responding; however, with repeated exposure to LPS, rats developed a behavioral tolerance to its anhedonic effects [216]. It has also been shown that LPS has an altered response in the OB model of depression with OB animals displaying a blunted increase in 5-HIAA in the nucleus accumbens compared with control animals. The resistance to LPS-induced activation of accumbal serotonergic activity may be due to impaired secretion of proinflammatory cytokines in response to LPS in the OB animals [217]. To further link inflammation to depression, studies have shown that antidepressants attenuate inflammation-induced

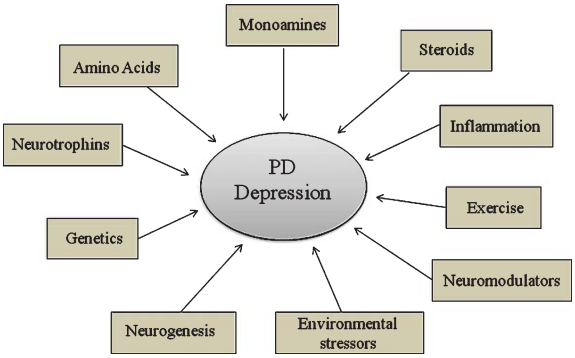

Fig. 1. Summary of different systems which could underlie depressive symptomatology in PD and have been studied in animal models.

cytokines production and action in the brain, which is associated with the reduction of depressive-like symptoms [218, 219]. In parallel, subchronic treatment with IL-1 was found to both reduce BDNF expression at both protein and mRNA levels and down regulate the TrkB receptor expression in the hippocampus [220]. Moreover, inflammation and cytokine expression have been shown to inhibit neurogenesis [221, 222] while immunomodulators have a concentration-dependent pro-neurogenic potential in the adult brain [223]. At the moment, no studies have examined the role of inflammation in animal models of parkinsonian depression.

REGULATION OF PD AND DEPRESSION BY DEEP BRAIN STIMULATION

Almost 100.000 PD patients have undergone deep brain stimulation (DBS) surgery, mostly targeting the subthalamic nucleus [224]. While beneficial against the motor symptoms of PD, it has become apparent that individuals who receive the treatment have an increased risk of suicide [225]. Studies in animal models of PD have demonstrated that subthalamic nucleus stimulation reduces the activity of the 5-HT system which could participate in the depression symptomatology [226]. In contrast, recent studies have demonstrated that DBS of the subgenual cingulate cortex [227] and the nucleus accumbens [228] can successfully alleviate depressive symptoms in non-PD patients with major depression that is refractory to medical treatments. Future animal studies may facilitate the identification of brain regions which upon DBS relieve both PD and depression.

EXERCISE AS TREATMENT OPTION IN DEPRESSION AND PD

Recent studies have demonstrated that exercise improves motor function in animal models of PD [229–231] or neuropsychiatric symptoms in normal mice [232]. The MPTP mouse model has been used to assess the potential positive effect of exercise on symptoms of depression in PD [233]. Unexpectedly, this study did not show any improvement in the sucrose preference test and in the TST [233]. Thus, it seems difficult to properly judge the effect of exercise on depression using the MPTP model.

CONCLUSIONS

Depression is a common non-motor symptom of PD. Despite the impact of depression on quality of life for PD patients, there is not much research done in animal models. Many tests of depression-like behavior in animals rely on locomotion and are not ideal for studies in PD models. However, some tests, including sucrose preference and NIH, are largely independent upon locomotion and can provide reliable data when studying a depressive-like phenotype in a PD model. There is also a need for the development of additional motor independent depression-related tests for animal models of PD. Since depression often is an early sign of PD, many acute models, such as the 6-OHDA model, are not ideal for depression-related studies. More progressive models of PD pathology have better construct validity and impressive studies on non-motor symptomatology have been performed using VMAT2 mutant mice. Changed in limbic DA, NA and perhaps 5-HT are involved in parkinsonian depression, but future work will probably also find important roles for additional factors, like amino acids and neurotrophins, and processes, like stress and inflammation.

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