NEUROBIOLOGICAL SIMILARITIES BETWEEN DEPRESSION AND PARKINSON'S DISEASE: ETIOLOGICAL AND THERAPEUTIC IMPLICATIONS

By

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Abstract

This literature review discusses the comorbidity of depression and Parkinson's disease and the possible implications for the etiology of depression given that it often occurs as a part of Parkinson's disease progression. The review contains descriptions and analyses of three popular hypotheses about depression etiology, including the monoamine hypothesis, the inflammation hypothesis, and the neuroplasticity or glutamate hypothesis. Each of these proposed mechanisms is compared with the physiology of Parkinson's disease to better understand why depression and Parkinson's disease may be comorbid from a neurobiological standpoint. The monoamine hypothesis and the neuroplasticity hypothesis of depression seem to best fit the characteristics of Parkinson's disease and provide the most cogent explanations of major depressive disorder. Furthermore, dopamine receptor agonists and ketamine are analyzed as interventions in depression and Parkinson's disease.

Introduction

Major depression is a common psychological disorder impacting 4.4% of the population, an estimated 322 million people as of 2015 (WHO, 2015). Despite the global prevalence and impact of major depressive disorder, the etiology of depression is not fully understood. However, comorbidity of depression and Parkinson's disease may provide insight into the mechanisms of action that may be at the root of both disorders, allowing for improved treatment of depression, especially in people with Parkinson's disease.

Parkinson's disease is a subtype of Lewy body dementia, which occurs when bundles of protein, mostly alpha-synuclein, accumulate in a neuron, leading to neuronal death. The Lewy bodies accumulate in certain areas of the brain, beginning within the olfactory bulb and migrating to the brainstem, including the serotonin-rich raphe nuclei and the norepinephrine-rich locus coeruleus. The most well-known neurological impact of Parkinson's disease is the extensive build up of Lewy bodies within the striatum, especially the dopamine-producing neurons of the substantia nigra, leading to a noticeable and often severe shortage of dopamine signaling within the brain (Jellinger, 2014).

Dopamine plays a role in a multitude of biological processes within the brain. In addition to being a part of the mechanisms of spatial memory, reward, pleasure, and motivation, dopamine is also a necessary neurotransmitter in regulating the motor cortex. The shortage of dopamine production in the brain of a Parkinson's patient leads to a variety of symptoms, including motor-related symptoms (tremors, slow movement, poor balance), apathy, and may even be partially responsible for depressed mood (Klein et. al., 2018). However, even though dopamine deficiency is the oldest and most common understanding of Parkinson's disease, there are symptoms and processes beyond the scope of dopamine deficiency alone. Nonmotor

symptoms such as sexual dysfunction, circadian rhythm dysregulation, and the many complicated layers of cognitive decline are not entirely accounted for by dopaminergic cell death alone. The exact molecular processes of Parkinson's disease are still not fully understood and appear to go beyond the simplistic explanation of dopamine deficiency (Jellinger, 2014).

That being said, Parkinson's disease provides an important opportunity in depression research because of the high instance of depression within Parkinson's disease. Examining the biomarkers of Parkinson's and people with major depressive disorder (MDD) may provide insight into the most likely physiological causes of depression. Comparing this data to the common hypotheses of depression emphasizes which hypotheses may be most accurate.

There are several hypotheses regarding the etiology of depression. One, which closely aligns with the current understanding of Parkinson's disease, is the monoamine hypothesis. The hypothesis states depression arises from a lack of sufficient monoamine signaling within the brain (Liu et. al., 2017). The monoamine hypothesis focuses on serotonin, dopamine, and norepinephrine, citing the efficacy of SSRIs (selective serotonin reuptake inhibitors), MAOIs (monoamine oxidase inhibitors), and SNRIs (serotonin and noradrenaline reuptake inhibitors) as evidence. Depressed patients are frequently found to have low blood levels of serotonin as well as low plasma levels of serotonin precursor L-tryptophan, though this is still debated by researchers, and serotonin has been implicated in processes that often go awry in depressed patients, including circadian rhythm and sexual function. Additionally, dopamine has been studied as a key player in anhedonia, the inability to experience pleasure, and norepinephrine has been implicated in emotional memory and emotional learning (Szczypiński & Gola, 2018; Terbeck et. al., 2016).

The monoamine hypothesis faces two primary critiques. The first is that common antidepressants, which mostly act to increase serotonin signaling, though some also increase norepinephrine signaling or even dopamine signaling in addition to serotonin, are not effective for all people with major depressive disorder (Hori & Kunugi, 2013). Another common critique is the delayed action of these antidepressant medications, often taking four to six weeks to begin alleviating depressive symptoms (Sanacora et. al., 2012).

A newer hypothesis, the inflammation hypothesis, is a recent and somewhat controversial hypothesis which states that depression may be a consequence of inflammation. The inflammatory hypothesis is distinct because it does not focus on a primarily neurological abnormality. Instead, it posits that an immune response leads to changes in gut microbiota composition, leading to a shortage of tryptophan, a serotonin precursor. This hypothesis is supported by data that shows depressed patients tend to have much higher cerebrospinal fluid levels of pro-inflammatory cytokines (Miller & Raison, 2016). Similarly, Parkinson's patients also have high CSF levels of these same pro-inflammatory cytokines, which may provide some support for the inflammation hypothesis of depression and explain the comorbidity of Parkinson's disease and depression (Prell et. al., 2019).

The final hypothesis examined in this literature review is the neuroplasticity hypothesis. The neuroplasticity hypothesis is intricate and examines glutamate and chronic stress as the two root mechanisms responsible for depression. Glutamate is heavily involved in the process of regulating neural connectivity, synapse strength, neural growth, and communication (Liu et. al., 2017, Reznikov et. al., 2011; Sanacora et. al., 2012). The neuroplasticity hypothesis essentially suggests that chronic stress allows glutamate to strengthen the neural connections active in a stressed brain. The efficacy of ketamine, an antagonist at the glutamate NMDA receptor, as a

rapid-acting antidepressant is one main piece of supporting evidence for the neuroplasticity hypothesis (Carlson et. al., 2013).

This literature review will examine physiological overlap between depression and Parkinson's disease to understand the validity of the monoamine hypothesis, the inflammation hypothesis, and the neuroplasticity hypothesis.

The Monoamine Hypothesis

Serotonin

Serotonin (5-HT) has long been at the center of conversations regarding depression etiology. This is primarily because of the efficacy of SSRIs, which operate by inhibiting the serotonin transporter (SERT). By inhibiting SERT, the reuptake of serotonin into a neuron is inhibited, resulting in an increase of serotonin signaling within the brain (Fakhoury, 2016). Other studies have supported the involvement of serotonin in depression, including studies demonstrating low blood 5-HT and tryptophan (a 5-HT precursor) levels in MDD patients (Ogawa et. al., 2014). Additionally, the serotonin system and the circadian system are hypothesized to be intricately involved in each other's regulation and normal functioning (Daut & Fonken, 2019). The involvement of serotonin within the circadian system is further evidence for the idea that MDD arises from serotonin dysregulation.

A 2017 study done by Ji *et. al.* examines the impact of aerobic exercise on depressive behaviors and 5-HT levels in rats with and without postpartum depression. The study provides compelling evidence that serotonin and tryptophan hydroxylase (an enzyme involved in 5-HT synthesis) deficiency play a role in MDD symptoms. At the beginning of data collection, the control group of rats and the group of rats with postpartum depression were given forced

swimming tests and open field tests to observe their depressive behaviors. After two weeks of the chosen intervention (either 30 minutes of running on a treadmill per day or no exercise), the rats were given the same forced swimming and open field tests. Immunohistochemistry was then used on the rat brains to measure 5-HT and tryptophan hydroxylase levels (Ji et. al., 2017).

The study demonstrated that not only can exercise increase 5-HT and tryptophan hydroxylase (TPH) levels within the brain, but also that 5-HT and TPH levels have an inverse correlation with depression symptoms. The results of this study may not be widely generalizable to humans with MDD, especially considering that the rats had postpartum depression, not MDD, and that measures of depressive symptomatology in rats are limited. However, the study does provide compelling evidence that symptoms of depression correlate with lower levels of 5-HT and TPH (Ji et. al., 2017).

In the pursuit of demystifying the connection between serotonin and depression, the 5-HT receptor proteins and SERT have been studied extensively. SERT tends to be a major therapeutic target and mutations in SERT functionality may even be responsible for the genetic component of MDD, as more SERT activity leads to less serotonin in the extracellular space and therefore less serotonin signaling (Fakhoury, 2016). Serotonin receptors may also be effective therapeutic targets in the future, though. The 5-HT_{1A} receptor is one serotonin receptor that remains an area of interest because of its possible role in MDD. The 5-HT_{1A} receptor can be presynaptic or postsynaptic. The presynaptic 5-HT_{1A} receptors are dense within the raphe nuclei, which contain serotonin-producing neurons, and serve as autoreceptors, regulating the level of serotonin signaling within the brain. When presynaptic 5-HT_{1A} autoreceptors are activated, the release of serotonin is inhibited (Nautiyal & Hen, 2017). 5-HT_{1A} receptors are also dense within the hippocampus and the cerebral cortex (Ito et. al., 1999).

This is all relevant to Parkinson's disease because, although the dopaminergic system tends to be the focus of PD research, the serotonergic system also degrades as PD progresses and may have some very interesting implications for depression in PD (Politis & Niccolini, 2015). PET studies using ^{11}C-DASB, which binds to SERT, demonstrate reduced levels of SERT within the basal ganglia and raphe nuclei in PD patients (Loane et. al., 2013, Politis & Niccolini, 2015). A 2020 study using ^{123}I-FP-CIT, which binds non-selectively to serotonin and dopamine transporters, demonstrated the same thing, showing reduced binding levels within the raphe nuclei of PD patients (Pasquini et. al., 2020). Notably, these studies also exhibit an inverse correlation between SERT levels and tremor severity in Parkinson's patients, further implicating serotonergic degradation as a hallmark of PD (Loane et. al., 2013; Pasquini et. al., 2020).

Another PET study by Ballanger *et. al.* examines levels of 5-HT$_{1A}$ receptors within the brain using [^{18}F]MPPF, a PET tracer used to image 5-HT$_{1A}$ receptors. Although the study utilized a small sample size, making the results less generalizable than preferred, the data demonstrates that PD patients take up significantly less [^{18}F]MPPF than healthy control groups. This means there is a decreased availability of 5-HT$_{1A}$ receptors in Parkinsonian brains, perhaps due to dysfunctional serotonin signaling, atrophy within the raphe nuclei, hippocampus, and cerebral cortex, or both dysfunction and neuronal atrophy at the same time.

Considering that degradation of the serotonergic system is a part of PD progression, it is no surprise that PD patients have lower levels of 5-HT$_{1A}$ receptors than the control. However, the data also shows that depressed PD patients had less [^{18}F]MPPF binding in the several areas of the brain than their non depressed counterparts (Ballanger et. al., 2012). These areas included the left hippocampus, associated with memory, the right insula, associated with motivation and desire, and the ventromedial prefrontal cortex, associated with decision-making. Because this was the

most noticeable difference between the depressed and non depressed PD groups, this finding implies that degradation of the serotonergic system in these areas may be responsible for some symptoms of depression.

The impact of Parkinson's disease on the serotonergic system supports the idea that serotonin dysregulation plays a large role in the etiology of depression and may be responsible for the comorbidity of the two disorders. Based on the literature, it appears that depression and PD share serotonergic dysregulation as a common feature.

Dopamine

The dopamine dysregulation hypothesis is not necessarily a hypothesis about depression alone. Instead, it suggests that dopamine dysregulation may cause several symptoms seen across psychiatric disorders. Schizophrenia, bipolar disorder, and depression have all been discussed within the context of the dopamine dysregulation hypothesis.

Most germane to MDD, however, dopamine dysregulation may play a large role in motivational anhedonia, one of the hallmark symptoms of MDD. Motivational anhedonia is the lack of desire and motivation to participate in pleasurable activities, not to be confused with consummatory anhedonia, which is the diminished ability to experience pleasure at all (Szczypiński & Gola, 2018). It has long been theorized that anhedonia comes from dysfunction within the reward circuit. The reward circuit is complicated, but several areas are most relevant for this discussion: the ventromedial prefrontal cortex, the striatum (including the nucleus accumbens, the caudate nucleus, and the putamen), the ventral tegmental area, and the substantia nigra. Both the ventral tegmental area and the substantia nigra contain high concentrations of dopaminergic neurons (Haber, 2017).

Several studies support the link between the reward circuit and motivational anhedonia and dysfunctional reward processing. Dopamine signaling within the striatum tends to be reduced in unmedicated depressed patients, however, when treated with amisulpride (a D2/D3 antagonist, which increases dopaminergic transmission by blocking presynaptic D2/D3 autoreceptors), patients demonstrate an increased striatal response when compared with their untreated counterparts. This increase in activation and functional connectivity correlates with improved reward learning and is most pronounced in the nucleus accumbens, a region implicated in motivation, aversion, reward, addiction, and impulsivity (Admon et. al., 2017). This study demonstrates that increasing dopaminergic signaling tends to also increase reward processing, something that is diminished in most cases of MDD, manifesting in the form of possibly both motivational and consummatory anhedonia.

Despite the alluring possibility that anhedonia, arguably the most debilitating symptom of MDD, may be mitigated by increasing dopamine signaling within the reward circuit, the most popular antidepressants are SSRIs and SNRIs. SSRIs (selective serotonin reuptake inhibitors) act by inhibiting serotonin reuptake and therefore increasing serotonin signaling. SNRIs (serotonin and norepinephrine reuptake inhibitors) have essentially the same mechanism of action, but act on both serotonin and norepinephrine reuptake. Neither of these popular classes of antidepressants appear to directly target dopamine.

However, even though SSRIs and SNRIs are popular, they are not an infallible cure for depression. Treatment-resistant depression (TRD) is a form of depression that does not subside after at least for weeks, often longer, of treatment with a therapeutic dose of an antidepressant. Unsurprisingly, the complaints of many TRD patients, as well as some MDD patients seeking SSRI or SNRI treatment, is that they have residual anhedonia (Cassano et. al., 2004).

Cassano *et. al.* conducted a study in which TRD patients were treated with pramipexole (a D2/D3 receptor agonist, commonly used to treat Parkinson's disease) in addition to a normal dose of a TCA (tricyclic antidepressant) or an SSRI. The study found that 68% of the participants were in remission after 16 weeks and 60.9% were in remission after a full year. Although the sample size of this study was small, the results suggest that treatment with a dopamine receptor agonist in addition to an antidepressant may help treat MDD (Cassano et. al., 2004).

These studies suggest that, while deficient dopamine signaling may not be the sole cause of every case of MDD, the role of dopamine in the reward circuit may make it an important part of depression symptomatology, namely anhedonia. This aligns very closely with the idea that PD progression can actually cause depression. PD at its core is mass atrophy and dysfunction of dopaminergic neurons within the substantia nigra (Jellinger, 2014), so if dopamine dysregulation is a cornerstone of anhedonia and impaired reward processing, it stands to reason that a patient with PD would almost definitely exhibit these hallmark symptoms of MDD.

Although the prevalence of depression in PD patients is unclear, research estimates it could be anywhere from 20-50% (Rihmer et. al. 2014). This estimate could be low because of the underdiagnosis of depression in elderly people, the fallibility of self-report measures, or the dismissal of MDD symptoms as the result of PD. However, if dopamine deficiency truly plays a role in depression symptomatology, the prevalence of depression in PD patients should be much higher.

This discrepancy demonstrates that MDD is not an easily understood disorder with one clear etiology. The fact that not all PD patients exhibit symptoms of depression supports the idea that depression may be an umbrella term for many similar-looking disorders that come about

differently. Dopamine dysregulation may be to blame for some patients' treatment resistant depression, just as dopamine dysregulation seems to be a clear explanation for anhedonia in Parkinson's disease. However, it is not logical to assume that every case of depression comes from dopamine dysregulation.

Noradrenaline

The studies examining the role of noradrenaline dysfunction and dysregulation in MDD are limited, especially in comparison to the wealth of literature about serotonin and dopamine. Therefore, more extensive research is needed before any solid conclusions can be reached. However, the current research on noradrenaline indicates that noradrenaline deficiency may be involved in some of the cognitive challenges MDD patients face.

The role of noradrenaline in depression is somewhat nebulous, but, like serotonin, many people with MDD rely on noradrenaline-based interventions. Although SSRIs are a common antidepressant, SNRIs, serotonin and noradrenaline reuptake inhibitors, and NRIs, noradrenaline reuptake inhibitors, are also used to treat MDD. The efficacy of these drugs is some evidence that noradrenaline signaling is involved in the development of MDD.

Noradrenergic neurons originate from the locus coeruleus (LC) within the brainstem and have been implicated in the sympathetic nervous system. It would appear that a normal stress response involves higher LC reactivity and enhanced noradrenaline signaling (Seki et. al., 2018), but noradrenaline does more than just elicit a stress response. The LC innervates the hippocampus, so it should be no surprise that noradrenaline may be important in memory formation (Zenger et. al., 2017). Stress also activates noradrenaline release within the amygdala and prefrontal cortex, suggesting its involvement in emotional processing and emotional learning (Terbeck et. al., 2016). The therapeutic use of propranolol, an anxiolytic and an antagonist at

noradrenergic β_1 and β_2 receptors, further supports the functionality of noradrenaline as part of the stress response and a key player in emotional memory. Propranolol is frequently used for anxiety-inducing situations such as job interviews and performances. It helps reduce the bodily response to stress, such as fast heart rate, and it reduces emotional arousal as well as emotional memory consolidation (Terbeck et. al., 2016).

The degradation of noradrenergic neurons is a well-documented feature of Parkinson's disease (Sommerauer et. al., 2015; Pifl et. al., 2012). Noradrenaline and dopamine deficiencies are both responsible for motor symptoms in PD (Pifl et. al., 2012), but given the importance of noradrenaline in memory and emotion-related cognition, noradrenaline deficiency may also play a role in the non-motor symptoms of Parkinson's disease, particularly cognitive and memory deficits.

Similarly, noradrenaline deficiency could be to blame for the same symptoms in MDD. MDD patients can experience cognitive challenges, difficulty paying attention, difficulty remembering, and feelings of apathy. Examining the role of noradrenergic signaling within the brain, these symptoms could be traced back to dysregulation within the noradrenergic system. However, more research is needed to truly understand the role of noradrenaline in MDD.

Conclusions

The monoamine hypothesis of depression closely aligns with the known physiology of Parkinson's disease. Parkinson's disease patients often experience significant deficits in serotonergic, dopaminergic, and noradrenergic signaling. If the monoamine hypothesis of depression does correctly describe the etiology of MDD, depression symptoms would be a logical byproduct of PD pathogenesis.

The Inflammation Hypothesis

The inflammation hypothesis of depression theorizes that MDD occurs as a consequence of chronic low-grade inflammation. Several studies have found that depressed patients exhibit higher levels of biomarkers used to measure inflammation (Miller & Raison, 2015). Such biomarkers include pro-inflammatory cytokine interleukin-6 (IL-6), chemokine interleukin-8 (IL-8), cytokine tumor necrosis factor (TNF), and C-reactive protein (CRP). These biomarkers are commonly used to measure immune response and have been demonstrated to be reliable indicators of inflammation in both the peripheral and central nervous system (Felger et. al., 2018).

The inflammation hypothesis theorizes that stress leads to inflammation and upregulation of pro-inflammatory pathways, which in turn activate the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis, consisting of the hypothalamus, the pituitary gland, and the adrenal glands above the kidneys, helps regulate several functions in the body. HPA axis activation has been implicated in anxiety and depressive behaviors and may alter the composition of an individual's gut flora. If gut microbiota becomes unbalanced, there can be a shortage of tryptophan, a serotonin precursor, within the body (Inserra et. al., 2018).

Ultimately, the inflammation hypothesis explains depression as a result of an immune response, but there remains a shortage of research establishing temporal precedence. A study done by Felger, Li, Haroon, Woolwine, Jung, Hu, and Miller *(2016)* demonstrates an association between inflammation and connectivity within the brain's reward circuit, but fails to determine which came first. In the study, unmedicated participants take several self-report questionnaires to assess their depressive symptoms, particularly anhedonia. Their inflammation levels are measured via plasma biomarkers, including CRP, IL-6, IL-1β, and TNF. In order to observe

connectivity between the ventral striatum (VS) and ventromedial prefrontal cortex (vmPFC), two areas involved in the reward pathway and emotional regulation, researchers took BOLD fMRI scans of participants. The study found that increased reports of anhedonia correlated with decreased connectivity between the vmPFC and VS, which in turn correlated with high levels of inflammatory biomarkers. Although these findings appear to support the inflammation hypothesis by showing that anhedonia, a hallmark of depression, correlates with high inflammation levels, the study has no data to support the idea that inflammation actually causes anhedonia. It is possible that the stress of depression and anhedonia themselves are actually to blame for high levels of inflammation (Felger et. al., 2016).

Other studies attempt to firmly establish temporal precedence, such as the 12 year follow-up of the Whitehall II study (Gimeno et. al., 2008). Although the study finds a very small association between inflammation levels at the earlier date and depressive symptoms at the later date, the study does little to account for a few important confounds. The study does not take into account the sociopolitical climate at each point in the study, nor does it track any data between the first data collection and the second data collection, which are an average of 12 years apart for participants. Not only did the study design neglect to take these important factors into account, but the final effect size is too small to bolster the claim that inflammation causes depression (Gimeno et. al., 2008). In fact, another longitudinal study, performed by Danese *et. al.* (2008), investigates the link between inflammation and depression only to find that a third variable, childhood mistreatment, may explain the correlation. Additionally, even if higher inflammatory biomarkers did, in fact, predict future depressive episodes, it would still be unclear if a third variable, such as chronic stress, was responsible.

Inflammation has also been studied extensively in the context of Parkinson's disease. Like MDD patients, PD tend to exhibit higher levels of inflammatory biomarkers than healthy control groups (Lindqvist et. al., 2012). Additionally, a Taiwanese study found that individuals with IBD (inflammatory bowel disease) were more likely to develop PD than their healthy counterparts, possibly indicating that chronic inflammation may be a risk factor for PD (Lin et. al., 2016). These results do provide compelling evidence that inflammation may cause PD and contribute to the non-motor symptoms of PD, including depression. Inflammation may be a part of the causal mechanism for depression in PD, but there does not seem to be enough evidence to state that inflammation causes MDD.

The Neuroplasticity Hypothesis

Glutamate and Neuroplasticity in Depression

The neuroplasticity hypothesis, like the monoamine hypothesis, was born largely from a fortuitous discovery of an effective antidepressant agent. In the case of the monoamine hypothesis, MAOIs, SSRIs, and SNRIs inspired further investigation into the role of monoaminergic systems in depression. However, these antidepressants have a delayed action, usually four to six weeks, that implies monoaminergic dysregulation may not be the root cause of depression, seeing as these drugs can all increase monoamine levels quite quickly. The rapid antidepressant action of ketamine, however, has introduced a new possible mechanism of MDD (Sanacora et. al., 2012).

Ketamine is an antagonist at the NMDA receptor, an ionotropic glutamate receptor, and it shows high antidepressant efficacy at low doses, implying that excessive glutamate signaling is likely involved in MDD symptoms (Reznikov et. al., 2011; Liebe et. al., 2018; Evans et. al.,

2018). Glutamate serves as the main excitatory neurotransmitter within the central nervous system and is the most abundant neurotransmitter by far, with up to 85% of CNS synapses being glutamatergic synapses (Sanacora et. al., 2012). Glutamate is toxic to neurons when it is too abundant in a synapse, so its activity is tightly regulated by glial cells, which quickly remove glutamate from the synapse and convert it into glutamine within the glial cell before transporting it back to the presynaptic neuron for reconversion into glutamate (Abdallah et. al., 2014). Glutamine is also a precursor for GABA, the main inhibitory neurotransmitter, so the whole cycle of glutamate, glutamine, and GABA production is intimately connected and tightly regulated (Sanacora et. al., 2012).

Glutamate is also closely related to neuroplasticity, hence its relevance in the neuroplasticity hypothesis of MDD. Glutamate signaling can release or inhibit brain-derived neurotrophic factor (BDNF), a protein involved in cell growth, but it also regulates synaptic strength through processes called long-term potentiation and long-term depression (Sanacora et. al., 2012; Murrough *et. al.,* 2017). Long-term potentiation and long-term depression are complicated biochemical processes that are not yet fully understood. The most basic explanation, called Hebb's rule, is that neurons that fire together wire together; high intensity firing across a synapse strengthens the synapse while disuse weakens a synapse (Malenka & Bear, 2004). Essentially, increased glutamate signaling will trigger changes in neuronal growth and synaptic strength.

The reason this all may be relevant to depression is that stress increases glutamate signaling, which in turn may be toxic to some neurons and may engender changes in synaptic strength in other neurons (Sanacora et. al., 2012). Acute stress increases glutamate levels in the prefrontal cortex and hippocampus, two areas that are often atrophied in depressed patients

(Duman et. al., 2019). This atrophy may be the result of excitotoxicity. Furthermore, stress activates the HPA axis, which is often implicated in mood disorders and anxiety disorders, and chronic activation due to chronic stress may strengthen the neural connections within the HPA axis, making it more sensitive and more active (Liu et. al., 2017). In the neuroplasticity model of depression, chronic stress increases glutamate signaling, atrophying certain areas of the brain (the hippocampus and the prefrontal cortex) and strengthening connections in others (the HPA axis), essentially leaving the brain "stuck" in a dysfunctional state of stress.

There is a growing base of evidence for the neuroplasticity hypothesis. For instance, glial cells seem to be altered or decreased in people with mood disorders, indicating possible regulatory issues within the glutamatergic and GABAergic systems (Duman et. al., 2019; Sanacora et. al., 2012). Additionally, a post-mortem study by Chandley *et. al.* (2014) found that MDD patients had higher expression of glutamate receptor genes, particularly the GRIN1 subunit of the NMDA receptor. The decreased synapse numbers and decreased BDNF levels in MDD patients also support the hypothesis that MDD patients have dysfunctional neuroplasticity (Duman et. al., 2019).

Glutamate and GABA in Parkinson's Disease

The role of glutamate in Parkinson's disease is not as clearly defined as the possible role of glutamate in MDD. However, there is plenty of research regarding the role of GABA in PD, and given the cyclical relationship between glutamate, glutamine, and GABA, dysregulation in one amino acid neurotransmitter often means dysregulation in the others (Abdallah et. al., 2014). When reading about GABA signaling in PD, it is important to remember that GABA is just one side of the coin.

The GABA-collapse hypothesis of PD theorizes that the Lewy bodies responsible for neurodegeneration come from GABA deficiency. GABA is the main inhibitory neurotransmitter in the brain, preventing neurons from firing, thus preventing an influx of Ca^{2+} and preventing the release of synaptic vesicles. A protein called alpha-synuclein (SNCA) is implicated in the release and maintenance of synaptic vesicles, and SNCA is the same protein that, when overabundant, can form neurotoxic Lewy bodies. The GABA-collapse hypothesis states that the excessive buildup of Ca^{2+} ions and SNCA protein, perhaps from lack of proper inhibitory action, results in the formation of Lewy bodies. (Blaszczyk, 2016).

Similarly, a study by Song *et. al. (2021)* found that PD patients have greatly reduced GABA levels in the upper brainstem before the neuronal death in the substantia nigra even begins to take place. This aligns with reports that depressive behavior, brought on by chronic unpredictable mild stress, correlates with decreased GABA release in mice (Ma et. al., 2016). Both PD and MDD may have low GABA signaling as a characteristic and a possible component of the causal mechanism.

As previously mentioned, GABA and glutamate levels are intimately related. Therefore, within the context of the GABA-collapse hypothesis, it seems that the low GABA levels of PD patients should be accompanied by high glutamate levels. It seems that this is a correct assumption. Glutamate levels tend to be consistently high across animal models of PD, and a study exploring the efficacy of electroacupuncture as PD intervention provides further evidence for this. The study used four groups of rats, including the healthy control group, the PD model control group, a PD group receiving electroacupunture in common acupuncture points, and a group receiving electroacupuncture in points of the body not considered acupoints. Though this study may have set out to confirm the efficacy of electroacupuncture, it also provides evidence

that glutamate levels negatively correlated with both dopamine neuron survival and coordination. The Parkinsonian rats with better motor coordination at the end of the experiment also had higher levels of dopaminergic neuron survival and lower levels of glutamate (Sun et. al., 2012). Another study, done on parkinsonian monkeys, found that glutamate receptor antagonist AFQ056 improved locomotion when administered alongside L-dopa, indicating that high glutamate levels may correlate with worsened symptoms or be a sign of dysregulation of synaptic plasticity (Grégoire et. al., 2011).

Based on the somewhat congruent reports of high glutamate and low GABA signaling within both MDD and PD, it seems plausible that both depression and PD may be caused by dysregulation in the glutamatergic and GABAergic systems. However, glutamate and GABA are both so abundant in the brain that this information does not provide an immediately obvious therapeutic target.

Discussion: Therapeutic Implications and Future Directions

Dopamine Receptor Agonists as Antidepressants

Subscribing to the monoamine hypothesis of depression, particularly in regards to the role of dopamine in anhedonia, it would seem that dopamine agonist drugs are a reasonable choice for those with treatment resistant depression (Cassano et. al., 2004). However, the most popular antidepressants on the market, SSRIs and SNRIs, target serotonin and norepinephrine, not dopamine. The number of dopaminergic antidepressants is actually surprisingly small.

Examining the side effects that can occur when disrupting the dopaminergic system, though, it is logical that pharmaceutical companies are in no rush to medicate depression with

dopamine agonists. The dopamine D3 receptor is abundant in the reward circuit and often implicated in addiction and impulsivity (Cassano et. al., 2004).

Thomas Moore *et. al. (2014)* examined the possibility of dopamine agonist drugs increasing compulsive or addictive behaviors, including pathological gambling and compulsive shopping. The study, rather than working with participants directly, analyzes records of adverse drug events reported to the United States FDA. The study found that 44.9% of the reported impulse control disorder events were associated with dopamine receptor agonists, particularly pramipexole and ropinirole, which have a high affinity for the D3 receptor. This study is not perfect, as it relies on self-report data regarding a possibly shameful issue, but it does shed some light on the importance of dopamine in impulse control. Additionally, in a previously discussed study, *Pramipexole in treatment resistant-depression: an extended follow-up* (Cassano et. al., 2004), some participants withdrew completely from the study because of the impulse dyscontrol and psychomotor agitation they faced, among other side effects. Together, these findings indicate that dopamine agonist drugs may not be a healthy choice for everyone, especially those already struggling with an impulse control disorder. Dopamine agonist drugs should likely go through more extensive research, especially in regards to impulsivity, before they can be an effective antidepressant for the public.

Efficacy of Ketamine Treatment for MDD and PD and Implications for Glutamate-Targeting Therapies

The rapid antidepressant action of ketamine is a somewhat recent discovery and seems to have opened up the conversation about the role of glutamate signaling in depression. Several studies have found that ketamine significantly improves mood in MDD patients as early as two

hours after administration, with antidepressant effects lasting, in some cases, up to two weeks (López-Gil *et. al.,* 2019; Evans *et. al.,* 2018; Murrough *et. al.,* 2017).

Ketamine has also become a subject of interest for Parkinson's disease researchers. One study, done by Fan *et. al., (2017)*, demonstrated that subanesthetic doses of ketamine alleviated PD symptoms in mouse models of PD. In this study, two groups of Parkinsonian mice (one group treated with ketamine, one group untreated) and one group of healthy control mice were tested for balance, coordination, and memory retention. Immunohistochemistry further demonstrated that ketamine-treated mice retained their dopaminergic neurons to a greater extent than the untreated PD models. Though both PD models displayed reduced numbers of dopaminergic neurons when compared to the healthy control group, this provides some evidence that ketamine may have a protective effect on the dopaminergic neurons.

However, it is important to acknowledge that it may not be simply the antagonist action at the NMDA receptor that makes ketamine effective in MDD and PD intervention. In fact, the Fan *et. al. (2017)* study proposes a very interesting mechanism for the neuronal-protective activity of ketamine, one that may not even be exclusive to glutamate pathways. In their study, Fan and colleagues examine autophagy, the process by which a cell isolates and degrades waste (Mizushima & Komatsu, 2011), by measuring the levels of autophagy-associated proteins (namely mTOR, LC3-II, Beclin1, Parkin, and PINK1). They found that both Parkinsonian model groups (ketamine-treated and untreated) had significantly lower LC3-II, Beclin1, Parkin, and PINK1 expression than the healthy control, with significantly higher levels of mTOR. The ketamine-treated PD model group had significantly higher LC3-II, Beclin1, Parkin, and PINK1 expression than the untreated PD model, with lower levels of mTOR. Essentially, both PD model groups exhibited abnormal levels of autophagy protein expression, but the ketamine-treated

group more closely resembled the healthy control. This indicates that dysfunctional or dysregulated autophagy may be a hallmark, and a possible intervention target, of PD.

This aligns with the previously discussed understanding that Parkinson's disease comes from an accumulation of Lewy bodies, which are abnormal aggregates of alpha-synuclein protein. In a healthy brain, these overabundant proteins would presumably be degraded through autophagy. With this in mind, it is possible that the neuro-protective effect of ketamine comes from the observed increase in expression of autophagy-related proteins (Fan *et. al.,* 2017), which may not necessarily be a direct result of NMDA receptor inhibition alone. This study provides some interesting insight into the possible functionality of ketamine in terms of increasing autophagy; however, given that ketamine is still a new intervention in PD, more research is necessary to make solid conclusions about its mechanism of action or even its efficacy in a variety of human populations.

The rapid antidepressant action also may not be a direct result of NMDA receptor inhibition. There are several ideas about why ketamine is such an effective and fast-acting antidepressant, one being that NMDAr inhibition prevents phosphorylation of eukaryotic elongation factor II. This increases BDNF expression and therefore neuronal growth, especially in the hippocampus, which tends to be atrophied in depressed patients (Murrough *et. al.,* 2017). Although this could definitely be an effective tool in treating depression, the fact that ketamine acts so quickly may indicate that neuronal growth is not the only piece of the ketamine puzzle.

Ketamine is an antagonist at the NMDA receptor, but it also has less potent actions on serotonin transporter (SERT) and norepinephrine transporter (NET). There is also evidence that inhibition of NMDA receptors on GABAergic neurons results in downstream glutamate release, which activates AMPA receptors (Stahl, 2013). In fact, AMPA receptor antagonism has been

demonstrated to block the antidepressant effects of ketamine (Murrough *et. al.*, 2017), something that has led some to believe that AMPA, not NMDA, is the key to the antidepressant action of ketamine.

Serotonin and noradrenaline may actually be at the heart of the rapid antidepressant action of ketamine, though. A review by López-Gil *et. al. (2019)* claims that SSRIs increase serotonin levels first in the raphe nuclei, which could lead to a downregulation of serotonin and explain the delayed action of SSRIs. However, while SSRIs act on the raphe nuclei first, López-Gil *et. al.* propose that ketamine increases 5-HT levels in the medial prefrontal cortex, not the raphe nuclei, so no downregulation occurs. This could explain the rapid antidepressant effect of ketamine, as it very quickly increases 5-HT signaling in the mPFC, which is intimately involved in cognition and emotional regulation (Xu *et. al.,* 2019), without increasing 5-HT signaling in the raphe nuclei.

All these findings may indicate that the neuroprotective and antidepressant actions of ketamine may not actually be a direct consequence of inhibition at the NMDA receptor. While ketamine has opened the door for exploration into other therapies that target glutamate signaling, the intricacies of ketamine function may have implications beyond glutamate signaling.

As far as future research is concerned, exploring how to increase serotonin signaling within isolated parts of the brain, such as the mPFC, may be worthwhile. Similarly, investigations into how to improve autophagic functioning by increasing relevant gene expression could also lead to helpful therapeutic interventions.

Lastly, there are some discussions about the safety of ketamine, especially in regards to potential for abuse and possible neurotoxic effects of ketamine on developing brains (Slikker *et. al.*, 2015; Yang *et. al.,* 2018). Before ketamine becomes a commonplace intervention for MDD,

there should be further investigation into the safety of ketamine use for adolescents and young adults with MDD. Additionally, there is a growing pool of research examining the efficacy of ketamine metabolites (S)-norketamine and (R)-norketamine as independent antidepressant agents, possibly with the same efficacy as ketamine but with decreased detrimental side effects. However, like ketamine itself, the mechanisms of action of both enantiomers of norketamine are still unclear (Yang *et. al.,* 2018). These two areas of research could be explored further to ensure therapeutic ketamine is safe, especially if young MDD patients will be using it.

Incidence of Depression in Parkinson's Disease: An Underestimate?

The current estimate of depression in PD patients is roughly 45% (Rihmer et. al., 2014), though there is no strong consensus on how prevalent depression actually is in PD patients. However, observing the pathogenesis of PD, it seems that even normal disease progression has deeply detrimental effects on the brain, especially the monoaminergic systems, that are likely to manifest as symptoms of depression. Examining the profound neuronal death within the serotonergic and dopaminergic systems in particular, the question "why are so many PD patients depressed?" no longer seems appropriate. Instead, a better question is "how are only 45% of PD patients depressed?"

One possible explanation for the incongruent incidence of depression in PD is that non-motor symptoms of Parkinson's often coincide with symptoms of MDD. For example, both disorders include apathy, sleep disturbances, and cognitive dysfunction as possible symptoms. A person with Parkinson's disease may demonstrate a wealth of depressive symptoms that fall under the umbrella of their Parkinson's diagnosis, leaving their depression undiagnosed and possibly unrecognized.

Another possibility is that PD patients are victims of a pervasive trend within the healthcare industry. Depression is often underdiagnosed in elderly populations for a variety of reasons (Allan et. al., 2014). The natural aging process, including slower movement, decreased energy, and changes in normal sleep patterns, may mask the same symptoms caused by depression. Additionally, symptoms of depression may be dismissed as the result of other preexisting health conditions.

Summary

Given that Parkinson's disease patients have a high incidence of depression, the monoamine hypothesis and the neuroplasticity hypothesis seem to be likely mechanisms of MDD. The monoamine hypothesis states that MDD stems from dysregulation in the serotonergic, norepinephrinergic, and dopaminergic systems, all systems that are deeply impacted in PD, possibly resulting in depression. Although the inflammation hypothesis presents plenty of data to demonstrate the correlation between MDD symptoms and inflammatory markers, researchers have yet to establish that inflammation precedes MDD symptoms and is not just a result of MDD symptoms. The neuroplasticity hypothesis, which focuses on chronic stress and glutamate as the cause of depression, aligns with the currently understood pathogenesis of PD. However, the name may be misleading, as glutamatergic and GABAergic dysregulation seems to better describe the essence of the neuroplasticity hypothesis.

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