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Review Article

Potential Benefits for Treating Parkinson's disease by Therapeutically Focusing on Group III Metabotropic Glutamate Receptors

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Abstract

The motor symptoms of Parkinson's disease (PD) can be effectively reversed by current medications used to treat the condition, such as dopamine agonists and L-DOPA. They don't, however, significantly slow down the underlying degradation of dopaminergic neurons in the Substantia Nigra Pars Compacta (SNc), and prolonged use is linked to side effects including dyskinesia brought on by L-DOPA. Therefore, there has been a lot of focus on developing substitute non-dopaminergic medications that could get around some or all of these issues. The discovery of Group III metabotropic glutamate (mGlu) receptors in the basal ganglia occurred ten years ago. The pre-synaptic terminals of basal ganglia pathways include one or more of these receptors (mGlu4, mGlu7, or mGlu8), whose hyperactivity is linked to both the creation of motor symptoms in Parkinson's disease (PD), as well as in the progression of SNc degeneration. The hypothesis that group III mGlu receptors are interesting targets for PD drug discovery stems from the findings that medications that stimulate these hyperactive synapses can decrease transmission across them. The function and possible target of group III mGlu receptors in the basal ganglia are thoroughly reviewed in this work. Group III mGlu receptors are strongly suggested as possible therapeutic targets for both symptom relief and neuroprotection in Parkinson's disease (PD) based on a wealth of data from in vitro research and animal models of the disease.

Keywords: Dopamine; Parkinson's disease (PD); Dyskinesia; Metabotropic glutamate

Introduction

Unmet treatment requirements in Parkinson's disease are a neurological ailment that is second most common after Alzheimer's disease. It is characterized by motor abnormalities, including a resting tremor, rigidity, postural instability, slowness of movement (bradykinesia), and trouble initiating movements (akinesia). In addition to these traditional motor symptoms, people with Parkinson's disease may also experience pain, depression, bladder problems, gastrointestinal issues, and other related issues that negatively impact their quality of life. While there is a growing acknowledgment and focus on these non-motor symptoms [1], this review will examine current developments in the targeting of group III metabotropic glutamate (mGlu) receptors to treat classical motor symptoms. The substantial's gradual degradation of dopaminergic neurons is mostly responsible for the motor symptoms compacta nigra pars (SNc). These midbrain neurons project to areas of the forebrain, particularly the striatum, where dopamine is released to control cortically driven firing in the basal ganglia thalamocortical motor circuits, so facilitating appropriate movement planning and execution. The goal of current PD treatments is to restore striatal dopaminergic transmission by using dopamine agonists like ropinirole or bromocriptine or the dopamine precursor L-DOPA. Unquestionably, the development of L-DOPA in the middle of the 1960s was a huge advancement, providing millions of Parkinson's disease sufferers with effective relief from early-stage motor symptoms across the globe. The variety of dopamine agonists that are now on the market also offers comparable symptom alleviation. But these medications are ineffective in stopping the gradual degeneration of dopaminergic neurons in the nigrostriatal tract, which is indicative of Parkinson's disease pathology. Patients' long-term health is impacted by this failure because higher drug dosages needed to stabilize worsening symptoms can have incapacitating side effects, such as psychosis, aberrant reward-seeking behavior, and L-DOPA-induced dyskinesia (LID), which is characterized by involuntary hyperkinetic movements of a choreic, dystonic, or ballistic nature [2]. As people age, PD becomes more common. The prevalence of Parkinson's disease (PD) rose with age from 0.6 (65-69 years) to 3.6 (80-84 years) in a European survey of over 15,000 adults 65 years of age and beyond [3]. Given the present revolution in world demographics, the by 2050, the percentage of people 60 and older is predicted to treble to 22% [4]. The World Health Organization has classified Parkinson's disease (PD) as a major public health concern that will significantly strain health care resources globally due to the accompanying expected rise in the condition's incidence. Finding non-dopaminergic alternative medicines for Parkinson's disease (PD) that can relieve symptoms, halt the disease's progressive degeneration, and potentially prevent dyskinesia is a priority, which makes sense given the shortcomings of present PD treatments. The role of abnormal firing of basal ganglia circuits to increasing nigral degradation and clinical symptoms in Parkinson's disease Due to the two primary basal ganglia motor routes' different dopamine receptor populations, the loss of striatal dopamine innervations in Parkinson's disease (PD) causes opposing downstream changes in firing of these motor pathways (Figure 1) [5,6]. In the direct pathway, decreased firing of GABAergic striatal efferents to the internal Globus Pallidus (GPi) and the Substantia

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Nigra Pars Reticulata (SNr), the output regions of the basal ganglia, results from lack of dopamine D1-like receptor stimulation. On the other hand, in the indirect pathway, increased firing in the GABAergic striatopallidal pathway results in a loss of the inhibitory drive that is normally maintained through dopamine D2-like receptor stimulation. This, in turn, reduces GABAergic drive. to the Subthalamic Nucleus (STN), which causes the glutamatergic STN efferent's to fire more often towards the SNr/GPi [7]. The motor deficiencies associated with Parkinson's disease (PD) are caused by the aberrant firing of direct and indirect circuits, which results in a net rise in prevailing glutamate levels in SNr/GPi and inhibition of thalamocortical feedback [8,9]. Hence, compensating for these pathways' hyperactivity may help reduce the motor symptoms associated with Parkinson's disease. In fact, the beneficial clinical results, such as the amelioration of motor deficiencies and the decrease in LIDs, observed with surgical techniques like sub thalamotomy, pallidotomy, or deep brain stimulation of the STN or GPi to successfully turn off the output regions of the basal ganglia, reinforce the assumption that there is a lot of potential for correcting aberrant firing, especially in the indirect pathway. Nevertheless, pharmaceutical methods of regulating these channels' firing would be significantly more widely used than surgical techniques. The STN transmits direct projections to the SNc in addition to the output regions of the basal ganglia (Figure 1) [10]. Thus, in parkinsonian conditions, increased STN activity may cause a corresponding increase in glutamate release in the SNcThis anticipated increase in glutamate release in the SNc is linked to the subsequent progression of cell death in PD, even though it is not believed to be the primary cause of the degeneration of dopaminergic neurons in PD, which is likely a multifactorial process involving mitochondrial dysfunction, inflammation, altered protein handling, and oxidative stress. In addition to treating the symptoms mentioned above, pharmacologically compensating for overactivity of pathways within the indirect basal ganglia circuit. The location and operational implications of group III mGlu receptors within the basal ganglia circuitry may potentially decrease the degeneration's course in Parkinson's disease. Preclinical research in rats demonstrates that nigrostriatal tract damage caused by the dopaminergic toxin 6-hydroxydopamine (6-OHDA) is lessened when the STN is inactivated by chemical lesioning (kainic acid) (Piallat et al., 1996) [11] back this recommendation. Based on their distribution, functionality, and favorable targeting observed in preclinical research thus far, group III mGlu receptors appear to be good candidates to fulfill these expectations Group III mGlu receptors are among the three classes of G-protein-coupled mGlu receptors that are present in the circuitry of the basal ganglia and have demonstrated potential as therapeutic targets for Parkinson's disease (PD) [12]. The nomenclature used here for these receptors complies with the Guide to Receptors and Channels published by the British Journal of Pharmacology. These three groups differ in terms of signal transduction, agonist and antagonist pharmacology, and sequence homology. Enhanced neuronal excitation and phosphoinositide hydrolysis result from the coupling of Group I mGlu receptors, such as mGlu1 and mGlu5, through Gq/11 [13]. The use of antagonists or negative allosteric modulators to block these receptors has shown a lot of promise in the therapy of PD and associated dyskinetic side effects in PD models in rodents and primates [14,15]. However, in some experimental models of Parkinson's disease (PD), activation of group II mGlu receptors (which include mGlu2 and mGlu3), which couple through Gi/Go and lead to inhibition of neuronal transmission, has also shown promise [16,17]. Nonetheless, group III mGlu receptors

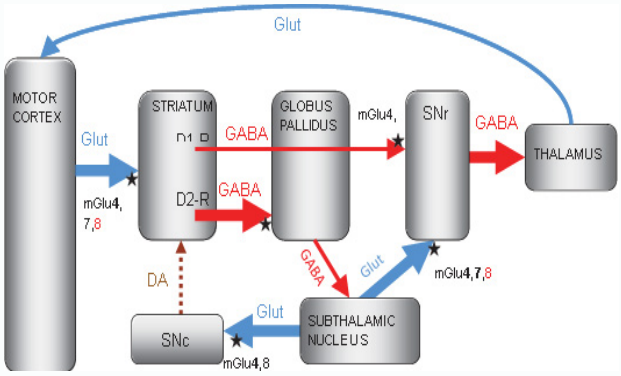

Figure 1: Schematic representation of the parkinsonian basal ganglia motor loop, showing the location of group III Metabotropic Glutamate (mGlu) receptors. The loss of striatal dopamine innervation following Substantia Nigra Pars Compacta (SNc) degeneration in Parkinson's disease (PD) produces opposing downstream changes in firing of the two main basal ganglia pathways. Thick lines indicate overactive pathways; thin lines indicate underactive pathways; dotted lines indicate degenerated pathways. In the direct pathway, loss of dopamine D1-like receptor stimulation reduces firing of GABAergic striatal efferent's to the substantia nigra pars reticulata (SNr), while in the indirect pathway, loss of inhibitory D2-like receptor stimulation leads to increased firing in the GABAergic striatopallidal pathway, which in turn inhibits GABAergic drive to the subthalamic nucleus (STN), leading to increased firing of the glutamatergic STN efferents to the SNr and SNc. The increased glutamatergic innervation of the SNr ultimately drives inhibition of thalamocortical feedback, resulting in the motor deficits seen in PD, while the increased glutamatergic innervation in the SNc may contribute to the progressive SNc degeneration. Group III mGlu receptors (mGlu4, 7 or 8), indicated by black stars, are found on pre-synaptic terminals of intrinsic basal ganglia pathways where their activation may serve to restrict transmitter release. Receptor subtypes indicated in bold have been confirmed as functional, while those in red have been shown to lack function. DA: Dopamine; Glut: Glutamate

are beginning to get more attention because to recent developments in drugs that target these receptors [18,19]. As a result, this study will offer a current, thorough summary of the data pertaining to group III mGlu receptor target potential in Parkinson's disease. Four subtypes of Group III mGlu receptors-mGlu4, mGlu6, mGlu7, and mGlu8—all have neuromodulatory roles, with the exception of mGlu6. the brain's functions [13]. Primarily present on the pre-synaptic terminals of GABAergic and glutamatergic neurons, these Gi/Go-coupled receptors play a role in modulating synaptic transmission by presumably inhibiting the voltage-gated calcium entry necessary to initiate transmitter release [13,20]. Additionally, these receptors have been shown at postsynaptic locations in specific brain regions, where it is anticipated that their signaling may cause membrane hyperpolarization by activating G-protein coupled inwardly rectifying potassium channels [21]. Through a combination of in situ hybridization, immunohistochemistry, and electron microscopy research, the location of group III mGlu receptors inside the basal ganglia has been partially elucidated. Of the three receptors of interest, mGlu4, 7 and 8) showing distribution that is primarily pre-synaptic. Figure 1 summarizes the distribution that has been accepted the most to date. Actually, in the past ten years, our knowledge of the location of mGlu4 and mGlu7 receptors has not altered all that much [22]. Although not covered above, the glutamatergic corticostriatal pathway is thought to be hyperactive in Parkinson's disease (PD) and consequently contribute to increased firing of the indirect BG pathway. Both mGlu4 and mGlu7 receptors have been discovered on the terminals of this pathway [9]. Additionally, GABAergic striatopallidal and striatonigral pathway terminals and excitatory (presumed) terminals have mGlu4 and mGlu7 receptors. terminals in

the SNr that are glutamatergic [23,24]. Although the SNr receives excitatory inputs from the STN as well as the frontal cortex and pedunculopontine nucleus [25,26], the expression of mGlu4 and mGlu7 mRNA on the terminals of STN efferents in the so-called subthalamonigral pathway is strongly supported by their presence in the STN [27,28]. Of all, the basal ganglia have the least well-characterized distribution of mGlu8 receptors. Although the cortex, striatum, and STN have been shown to express mRNA encoding mGlu8 receptors [28], our unpublished research indicates moderate to high levels of similar mGlu8 immunoreactivity in the SNr and striatum. Thus, it's still possible that pre-synaptic terminals of the corticostriatal, striatonigral, or subthalamic pathways include mGlu8 receptors. While group III mGlu receptors in the basal ganglia are thought to be mostly pre-synaptic, extremely low levels of mGlu7 immunoreactivity have been discovered at post-synaptic dendritic locations in the striatum and GP [23]. Nevertheless, no indication of a post-synaptic action of group III mGlu receptors in the GP was revealed by electrophysiological experiments [29], and it is unknown whether there is a post-synaptic action in the striatum. Thus, the potential of the pre-synaptic receptors is still the main emphasis at this time. Although the presence of group III mGlu receptors on pre-synaptic terminals of PD overactive pathways (corticostriatal, striatopallidal, and subthalamic) are a promising development. To support these receptors' potential as therapeutic targets for restoring basal ganglia pathway activity in PD, it is necessary to show that each receptor functions to regulate transmission across these synapses. Investigating the activities of subtype-selective agonists has been the only option left as subtype-selective antagonists are not readily available. Nevertheless, the development of subtype-selective agonists in the group III mGlu field has proven challenging, and the first subtype-selective agent was identified only in 2003 [29,30]. In this case, the agent was N-phenyl7-(hydroxylimino) cyclopropa[b] chromen-1acarboxamide (PHCCC), a positive allosteric modulator (PAM) of mGlu4 receptors the selectivity of PHCCC as well as that of the other substances covered below that have been utilized to pharmacologically investigate the functions of group III mGlu receptors in the basal ganglia. A multitude of electrophysiological data now suggests that group III mGlu receptors generally have a functional role in each of the target routes. The receptors in Figure 1 that have been shown to function are highlighted in bold. First, the corticostriatal pathway: it has been demonstrated that using the broad-spectrum agonists L-serine-O-phosphate (L-SOP) and L-2-amino-4-phosphonobutyrate (L-AP4) to activate group III mGlu receptors mediates the depression of striatal excitatory post-synaptic potentials (EPSPs) evoked by cortical stimulation [31,32]. It is believed that the suppression of glutamate release from corticostriatal terminals is the cause of this reduction of EPSPs. Slices from mGlu4 knockout animals did not exhibit these effects, but the new mGlu4 orthosteric agonist (3S) did in normal slices.-3- [hydroxymethyl-(3-amino-3-carboxypropyl(hydroxyl)-phosphinyl)] Cuomo et al. [32] reported that -5-nitrothiophene (LSP1-3081), suggesting that mGlu4 receptors are important mediators of this action. In contrast, cortically induced EPSPs in the striatum were not inhibited by the mGlu8-selective agonist (S)-3,4-dicarboxyphenylglycine ((S)-DCPG), indicating that mGlu8 receptors, if potentially present, are not functional at this synapse [32]. It is yet unknown what part putative mGlu7 receptors play in the corticostriatal circuit. Moving on to the striatopallidal pathway, it was found that L-AP4 mediates the inhibition of striatalevoked inhibitory post-synaptic currents (IPSCs) recorded in the GP [29,33]. This effect is probably explained by inhibiting GABA release from striatopallidal terminals, which was suggested by the distribution studies. Our *in vivo* micro dialysis investigations complement this by showing that local infusion of L-SOP or L-AP4 suppresses GABA release in [34] the rat GP. Since the L-AP4-mediated inhibition of IPSCs was lost in slices from mGlu4 knockout mice [33], but was enhanced in normal slices by the mGlu4 PAM PHCCC (Marino et al., 2003) [29] and mimicked by the novel mGlu4 selective agonist LSP1-2111 [35], the mGlu4 receptor appears to be crucial in the striatopallidal pathway. Despite the fact that mGlu7 receptor participation seems implausible given the decrease of L-AP4's effectiveness in animal slices with mGlu4 knockouts [33]. At this point, it is impossible to rule out a functional role for these receptors until the effects of mGlu7 selective drugs have been investigated. Electrophysiological evidence also confirms the existence of functioning group III mGlu receptors on terminals of the subthalamonigral pathway, which is consistent with the distributional data. Therefore, L-AP4 inhibits EPSPs in dopaminergic neurons of the SNc [34,36,37] and depresses STN-evoked EPSCs in the SNr [38,39]. Both effects are most likely due to reduction of glutamate release from STN terminals in both locations. To bolster this, we discovered that *in vitro*, L-SOP and L-AP4 blocked the depolarization-induced release of [3 H]-D-aspartate from rat SN slices, and that local *in vivo* glutamate release in the SNr was decreased by intranigral infusion of L-SOP [40]. Since the mGlu4 PAM PHCCC suppressed STN-evoked EPSCs in dopaminergic neurons of the SNc, mGlu4 receptors have once again been identified as one of the functional subtypes [41]. This is in line with what we discovered, which is that PHCCC increases the inhibition of [3 H]-D-aspartate release in SN slices mediated by L-AP4. Since the mGlu7 allosteric agonist N,N'-dibenzhydryl-ethane-1,2-diamine dihydrochloride [42] inhibits [3 H]-D-aspartate release in SN slices, our preliminary data suggest that these receptors act to inhibit glutamate release in the SN, even though no published reports have looked into the effect of stimulating mGlu7 receptors on STN terminals. Conversely, a Given that stimulation of mGlu8 receptors with (S)-DCPG neither reduced STN evoked EPSCs in the SNc [41] nor hindered [3 H]-D-aspartate release in our preliminary findings, a role for pre-synaptic mGlu8 receptors appears improbable. One possible reason for concern is the presence of group III mGlu receptors on GABAergic striatonigral terminals. These receptors have been demonstrated to mediate the suppression of striatal-evoked IPSCs in the SNr when activated by L-AP4 [39]. Studies focusing on individual subtypes have not been conducted to determine which group III receptors are the guilty ones. However, from a therapeutic perspective, these receptors represent a potential roadblock since inhibiting GABA release in the SNr would worsen stratocirrus transmission, which is already impaired, and may reverse the beneficial effects of preventing the release of glutamate from STN terminals in this area. Thankfully, available data appears to rule out any potential negative impact of turning on these receptors in Parkinson's disease. According to electrophysiological studies, L-AP4 can still inhibit STN-evoked EPSCs in the SNr when dopamine depletion, i.e., slices taken from animals treated with reserpine to deplete all catecholamines, but it can no longer inhibit striatal-evoked IPSCs in the SNr [39]. These results suggest that the pharmacological effects of group III mGlu receptors on the desired subthalamonigral terminals are likely to supersede those of the receptors on stratocirrus terminals when parkinsonian circumstances are present. The behavioral research in animal models of Parkinson's disease (PD) that is detailed below seems to support this assumption. Activation of these receptors has been predicted to alleviate parkinsonian symptoms by normalizing firing within the

basal ganglia circuitry and to provide protection against SNc degeneration by reducing glutamate-mediated excitotoxicity, since one or more functional group III mGlu receptor subtypes have been identified at several desirable locations in the basal ganglia circuitry [12,22]. This review's remaining sections will concentrate on recent data that has been gathered to validate these hypotheses.

Symptomatic Improvement after Activation of the Group III mglu Receptor Group III mglu Receptor

Targeting for symptomatic alleviation has been investigated in several animal models of Parkinson's disease. A systemic injection of reserpine depletes the brain of all monoamines, including dopamine, in the rat treated with it. Within 12 to 18 hours, akinesia is induced and maintained for up to 48 hours. Drug-induced akinesia reversal is tracked as a measure of symptom relief effectiveness. The systemic injection of haloperidol in rats causes a transient state of catalepsy, which is considered to be a sign of the symptomatic efficacy of test medications when it reverses. Lastly, akinesia in the forelimb contralateral to the lesion is evident in the unilateral 6-OHDAlesioned rat and manifests as decreased reaching in cylinder reaching tests. The reversibility of this akinesia is considered a symptomatic efficaciousness of the medicine. Neurochemical or electrophysiological findings in the basal ganglia output regions, the SNr or entopeduncular nucleus (the rat homologue of GPi), support features of increased STN firing and increased glutamate release, thereby supporting the validity of all three models [7,43,44]. Due to the scarcity of systemically active group III mGlu receptor agonists, or PAMs, most research has looked at the effectiveness of agents managed centrally. Site-directed injections have been particularly helpful in identifying which parts of the basal ganglia circuitry can be targeted to mediate favorable effects, notwithstanding their limited therapeutic relevance. All of these areas have been studied to some extent because pre-synaptic group III mGlu receptor activation in the striatum, GP, or SNr may limit transmitter release from hyperactive pathways to normalize firing of the basal ganglia circuits and so restore movement.

Focusing on the striatum

Broad spectrum group III mGlu agonists (1S,3R,4S)-1aminocyclopentane1,3,4-tricarboxylic acid (ACPT-I) and L-AP4 have been shown to alleviate akinesia in the 6-OHDA lesioned rat or to relieve haloperidol-induced catalepsy. These findings align with the L-AP4-mediated suppression of cortical-evoked EPSPs in the striatum [31], suggesting that the alleviation of symptoms is probably due to glutamate release inhibition from hyperactive cortical inputs. According to Cuomo et al. [32], nigrostriatal injection of the orthostatic mGlu4 agonist LSP1-3081 lowers akinesia in the 6-OHDA lesioned rat, supporting the electrophysiological findings that mGlu4 receptors are involved in this action. Despite the likelihood that mGlu8 receptors are not active in this area, given Considering their lack of functional effects as mentioned previously [32], it is still unknown whether mGlu7 receptors have any beneficial benefits. Going after the GP One of the first areas identified as mediating the broad-spectrum group III mGlu agonists' anti-parkinsonian effects was the GP. Research conducted in our lab initially showed that a rat given reserpine had akinesia that was reversed by directly injecting L-SOP into the GP [35]. Subsequent research has confirmed that correcting reserpine-induced akinesia, haloperidol-induced catalepsy, and 6-OHDA-induced forelimb akinesia can be achieved with direct intrapallidal injections of the broad-spectrum agonists, L-AP4 or ACPT-I. Treatment with group III mGlu receptor antagonists blocked these effects when evaluated, and these results most likely represent inhibition. Of GABA release in the GP [29,33,35], which is expected to return motor function by restoring normal firing within the indirect basal ganglia route. According to earlier electrophysiological studies [29,33], the most recent findings support the importance of mGlu4 receptors in the GP. Thus, in the 6-OHDA lesion rat model of Parkinson's disease, Beurrier et al. [36] showed that administration of the mGlu4 agonist, LSP1-2111, restored akinesia. However, intrapallidal injection of the mGlu8 agonist (S)-DCPG proved ineffective [36], ruling out any target, which is consistent with the absence of conclusive evidence favoring the existence of mGlu8 receptors on striatopallidal terminals. Here, the potential of mGlu8 receptors. Once more, confirmation of mGlu7 receptors' involvement in the GP is pending. Concentrating on the pars reticulata substantia nigra. As was previously mentioned, group III mGlu receptors are present on both the GABAergic striatonigral terminals and the intended glutamatergic subthalamic terminals inside the SNr. This suggests that activation of these receptors may result in a variety of effects, such as functional stale-mate with neither effect predominating, a net inhibition of glutamatergic transmission (i.e., inhibition of glutamate-evoked EPSCs), or a net inhibition of GABAergic transmission (i.e., inhibition of striatal-evoked IPSCs). Under dopamine depletion, Wittmann et al. [39] had demonstrated *in vitro* that group III mGlu receptors' favorable ability to block STN-evoked EPSCs in the SNr outweighed the potentially harmful effect to block IPSCs produced by striatal stimulation. Thankfully, it seems that this behavior occurs *in vivo*. Injections of broad-spectrum group III agonists, such as L-SOP, L-AP4, or ACPT-I, into the SNr produced beneficial anti-parkinsonian actions in conditions of marked dopamine depletion or dopamine receptor blockade. These actions included reversing akinesia induced by reserpine [35,40] and catalepsy induced by haloperidol. These responses most likely represent receptor-mediated regulation of glutamate release from hyperactive subthalamic neurons, given the electrophysiological, release, and microdialysis findings discussed above. Nevertheless, as seen *in vitro*, injection of ACPT-I into the SNr produced catalepsy in normal mice, likely due to a predominant impact to suppress GABA release from the striatonigral pathway. With some worry, Intranigral injections of ACPT-I also made akinesia worse in a partial 6-OHDA lesioned rat model of Parkinson's disease (PD) showing a (58%) reduction in striatal dopamine innervation. This suggests that the detrimental effects on GABAergic transmission remain predominant even with this degree of dopamine loss. There is considerable variation in the threshold degree of nigrsotriatal tract degeneration thought to be necessary for patients to experience symptoms. Some estimates place the latera's cell loss at 68%. When symptoms first appear, the ventral tier of the SNc (average 52% throughout the SNc). Some researchers have calculated that striatal dopamine transporters are decreased by 25% to 64% at the onset of symptoms based on positron emission tomography or single photon emission tomography [45]. Predicting the expected result of targeting group III mGlu receptors in the SNr during the early stages of Parkinson's disease is challenging due to this diversity. Determining whether group III mGlu receptor subtype, or at what stage of lesion development, the favorable effects of targeting group III mGlu receptors in the SNr replace the detrimental ones, will undoubtedly be crucial. May be to blame for the negative consequences before the entire significance of this discovery is understood. Given the failure of intranigral injection of the mGlu8-selective agonist (S)-DCPG to reverse haloperidol-induced catalepsy and the lack of *in*

vitro efficacy of (S)-DCPG in the SN [41], it is unlikely that the subtype of group III mGlu receptor mediating these anti-parkinsonian effects in the SNr is mGlu8. But the mGlu4 and mGlu7 receptors are still potential targets in the SNr, and our initial research—which shows that intranigral injections of the mGlu4 PAM, PHCCC, and the mGlu7 allosteric agonist AMN082 alleviated reserpine-induced akinesia-supports more research into these receptors' potential as therapeutic targets. Targeting several locations at once. As though Site-directed injections have provided valuable insights into the regions of the basal ganglia where activating group III mGlu receptors may have symptomatic potential in Parkinson's Disease (PD); administration routes that can target multiple sites simultaneously provide a more accurate picture of how these discoveries are likely to be translated into treatment approaches. Several animal models of Parkinson's disease (PD) have shown encouraging results thus far after intracerebroventricular (I.C.V.) treatment of group III drugs. The initial research of this type showed that intraperitoneal injections of the broad-spectrum agonists L-AP4 or L-SOP were effective in treating reserpine-induced akinesia, catalepsy caused by haloperidol, and forelimb akinesia in rats lesioned with 6-OHDA [33,35]. Importantly, how far the forelimb asymmetry is reversed generated by L-AP4 when administered by this method was comparable to that of L-DOPA, the gold standard medication for treating Parkinson's disease, strengthening the possibility of a beneficial clinical result with this strategy in the future. Only a portion of the receptor subtype(s) controlling the responses after intravenous injection has been identified thus far. PHCCC was reported to counteract reserpine-induced akinesia after intracerebroventricular injection [29], suggesting that mGlu4 receptors were potential targets for anti-parkinsonian relief. Studies demonstrating a comparable reversal of haloperidol-induced catalepsy and reserpine-induced akinesia after intravenous injection of the novel mGlu4 PAM (+/-)-cis-2-(3,5,dichlorphenylcarbamoyl)cyclohexane carboxylic acid (VU0155041) have provided additional evidence in favor of targeting mGlu4 receptors [19]. From a therapeutic standpoint, the most promising are the findings from research that use systemic delivery methods. It was initially demonstrated by Battaglia et al. [46] that reserpine-induced akinesia could be reversed by systemic delivery of the mGlu4 PAM PHCCC. Since then, it has been demonstrated that systemic injection of the new mGlu4 orthosteric agonist LSP1-2111 [36] and the broad-spectrum agonist ACPT-I (Lopez et al., 2008) can correct haloperidol-induced catalepsy. Although systemic administration of a mixed mGlu8 agonist/AMPA antagonist (R,S)-3,4-DCPG increased haloperidol-induced catalepsy, it is unclear if selective mGlu7 or 8 agonists (or PAMs) can alleviate symptoms in animal models of Parkinson's disease after intracerebral injection [47]. Although this result calls into question the ability of mGlu8 receptors to prevent Parkinson's disease, conclusions must wait until investigations with "cleaner" mGlu8 agonists have been initiated.

Group III mGlu Receptor Activation Provides Neuroprotection

Targeting group III mGlu receptors may be a viable therapeutic option for PD, as evidenced by the observation that broad spectrum group III mGlu agonists, such as L-AP4, can inhibit glutamatergic drive to the SNc [34] and the suggestion that glutamate-mediated excitotoxicity plays a role in the progressive SNc degeneration in PD [48,49]. While just a small number of studies have looked into the possible preventive benefits of group III mGlu receptor activation in PD animal models, all of them have produced encouraging results. According to research by Vernon et al. [50,51], infusions of the group III mGlu agonist L-AP4 into the rat SNc 1 6-OHDA-induced nigrostriatal tract injury can be prevented for three or seven days following the toxin. the generation. Concomitant administration of a group III mGlu receptor antagonist reversed the beneficial effects, indicating that they were receptor-mediated. These effects included preservation of striatal dopaminergic neurone markers, such as Tyrosine Hydroxylase (TH), protection of TH-positive cells in the SNc, and preservation of striatal dopamine content. Recent research conducted in our lab has validated the protective effect of sub-chronic L-AP4 treatment against 6-OHDA-induced nigrostriatal tract degeneration. It has also shown that this treatment regimen preserves the animals' motor behavior [40]. While these findings did not investigate the identity of the receptor subtype mediating this protection, our preliminary results suggest a function for mGlu4 receptors, as the mGlu4 PAM, VU0155041, protects against a comparable 6-OHDA lesion, maintaining in addition to preventing the loss of motor function, dopaminergic neuron markers in histology and neurochemistry are also present [52]. This result is in line with that of Battaglia et al. [52], who discovered that systemic injections of the mGlu4 PAM PHCCC, administered 30 min prior to toxin injection, provided approximately 50% protection against the loss of striatal dopamine content and decrease in the number of TH-positive cells in the SNc in mice caused by 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP). Similar protection against MPTP-induced degeneration was observed in this MPTP research after PHCCC was injected straight into the GP. This result suggests that the SNc may play a role in the normalization of glutamatergic drive, either directly through actions within the SNc or indirectly through GP firing correction and subsequent downstream reductions in STN glutamatergic drive to the SNc, in these animal PD models, can result in therapeutic alleviation. Research on the neuroprotective effects of mGlu7 or mGlu8 receptor activation as well as studies on the protective effects of systemic group III modulator administration are now highly anticipated.

Possible Processes That Underlie Neuroprotective Benefits

Based on available data, many hypotheses are put up to explain what processes might be involved in group III mGlu receptor-mediated neuroprotection (Figure 2). The transmitter release and electrophysiological results unquestionably indicate that one of the main influences is either direct or indirect suppression of glutamate release in the SNc. Nevertheless, several more concrete answers have emerged from *in vitro* investigations aimed at exploring the mechanisms behind protection provided by group III mGlu receptors. This discussion will mostly center on studies conducted in primary Ventral Mesencephalic (VM) cultures, which comprise TH-positive, dopaminergic neurons, even though many early insights were obtained from investigations conducted in other cell types, such as cortical or hippocampal neurons. Based on their research, the most convincing alternate theories involve group III mGlu receptor activation on either the glial cells that support the SNc neurons or the SNc neurons themselves. Thus far, rat brain microglia that lacked mGlu7 receptor expression [34] and primary cultured rat astrocytes have been found to express mGlu4 and mGlu7 receptors [53,54]. It is well known that glial mediators toxic to dopaminergic neurons, including as glutamate, nitric oxide, and hydrogen peroxide, are released when astrocytes are exposed to activators such Lipopolysaccharide (LPS) [55]. In fact, it has been demonstrated that in primary VM cultures, conditioned

media from LPS-treated astrocytes can induce apoptosis or neuronal cell death [53,56]. Significantly, Zhou et al. [53] discovered that VM cultures are shielded against LPS-conditioned medium-induced apoptosis when LPS-treated astrocytes are concurrently exposed to the broad-spectrum group III mGlu receptor agonist L-AP4. L-AP4 was also discovered to improve glutamate re-uptake in the astrocytes that were treated, which resulted in an increase in the antioxidant reduced glutathione levels in the astrocytes [53]. Moreover, MPTP-induced dopaminergic neuron degeneration is linked to astrocyte activation. Therefore, midbrain neuronal cultures were hazardous to conditioned media from astrocytes exposed to the poisonous pyridinium ion 1-methyl-4-phenylpyridinium (MPP+) [53]. Similar to LPS, it was discovered that MPP+ decreased astrocyte glutamate uptake, and concurrent exposure to L-AP4 was once more able to increase astrocyte glutamate levels absorption and lessen the conditioned medium's toxicity [53]. Therefore, one important mechanism supporting the neuroprotective potential of group III mGlu receptor activation may involve lowering the prevailing glutamate levels in the SNc by increasing glutamate reuptake into surrounding astrocytes. Remarkably, it has been demonstrated that the glial glutamate transporters GLT-1 and GLAST are up-regulated by the related group II mGlu receptors, which also couple through Gi/o, via a pathway that is dependent on Phosphatidyl-Inositol-3 (PI-3) kinase and Mitogen-Activated Protein (MAP) kinase [57]. In cultured cerebellar granule cells, L-AP4-mediated stimulation of group III mGlu receptors has also been demonstrated to activate MAP kinase and PI-3 kinase pathways. Therefore, it is possible that the enhanced astrocyte glutamate uptake observed in the aforementioned studies is due to a comparable up-regulation of glial glutamate transporters. According to research by Besong et al. [54] astrocyte cultures from mGlu4 -/- mice no longer exhibit the reduced production of proinflammatory chemokines when treated with L-AP4. This suggests that activating astoglial mGlu4 receptors may have additional anti-inflammatory benefits. Given that gliosis and inflammation are widely acknowledged as characteristics of PD pathogenesis [58], even though these processes have not yet been investigated in animal models of PD, it is highly plausible that the overall protective potential of targeting astroglial group III mGlu receptors in Parkinson's Disease (PD) is influenced by a component resulting from their activation. A study by Jiang et al. [59] revealed that L-AP4 may shield TH-positive neurons in rat embryonic midbrain cultures from rotenone's toxicity, which is the remaining, and, no doubt, more contentious piece of the mechanistic jigsaw. According to Ren et al. [59], rotenone has the ability to promote depolymerization of microtubules and block mitochondrial complex I, which includes MPTP. This last function is crucial in explaining rotenone's lethal effect on dopaminergic neurons. Rotenone has lately been utilized to induce dopaminergic neuron death both *in vitro* and *in vivo*, despite being less commonly employed than MPTP or 6-OHDA vivo [60]. Since L-AP4 increased activation of the MAP kinase extracellular signal-regulated kinase in these midbrain TH-positive neurone cultures and the protection against rotenone toxicity was blocked by pharmacological inhibition of MAP kinase kinase, the protective effects of L-AP4 against rotenone toxicity once again appeared to involve activation of the MAP kinase pathway (Jiang et al., 2006). The authors concluded that L-AP4 protected midbrain TH-positive neurons by activating the MAP kinase pathway to stabilize microtubules, as inhibition of MAP kinase kinase also prevented L-AP4-induced attenuation of rotenone-induced microtubule depolymerization. This work is especially intriguing because it shows that the cells were cultured in a media enriched with cytosine arabinoside, which suppresses the proliferation of glial cells. For the first time, research indicates that neuroprotection can be provided by specifically targeting group III mGlu receptors on the dopaminergic neurons themselves, as opposed to glial cells nearby or even the pre-synaptic terminals of incoming glutamatergic neurons. Regarding a possible post-synaptic activity of group III mGlu receptors in the SNc, not much is known to date. A post-synaptic presence for mGlu4 or mGlu8 receptors cannot be completely ruled out, as mRNA [28] and immunoreactivity for each have been reported in this region. Current evidence rules out the presence of mGlu7 receptors in the SNc [with negligible mRNA or mGlu7 immunoreactivity detected in the SNc [28]. But according to Wigmore and Lacey [34] despite seeing the previously described suppression of STN-evoked EPSCs in the SNc, indicative of L-AP4's pre-synaptic activity, it was not possible to identify any direct post-synaptic effects of the protein on SNc neurons. Further electrophysiological investigations by Valenti et al. [41] also ruled out the possibility that L-AP4 regulates SNc neuronal excitability in a post-synaptic manner. Therefore, more research is needed to determine whether modulation of neuronal excitability or any other post-synaptic activity that may be related to this possible neuroprotective impact could be mediated by mGlu4 or mGlu8 receptors.

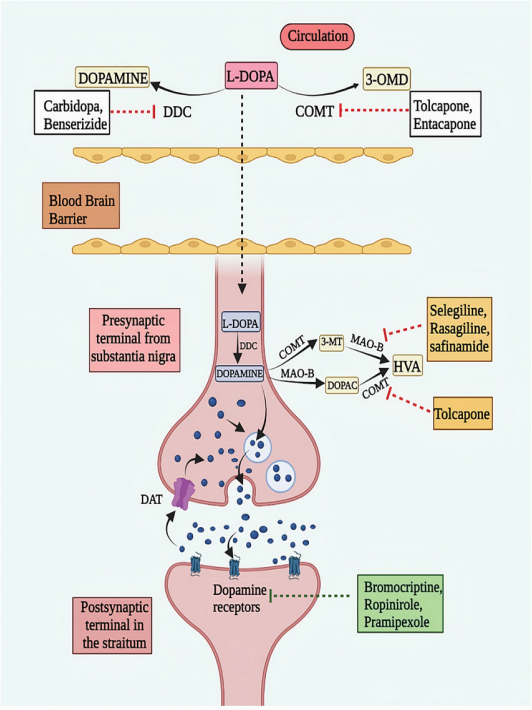

Figure 2: Mechanism of action of Drugs which are used in Parkinson's disease. COMT catechol-O-methyl transferase, DA dopamine, DDC dopa-decarboxylase, DOPAC 3,4-dihydroxyphenylacetic acid, HVA homovanillic acid, L-DOPA levodopa, MAO-B monoamine oxidase B, 3-MT 3-methoxytyramine, 3-O-MD 3-O-methyldopa, DAT: Dopamine Transporter.

Future Courses

The development of debilitating, excessive involuntary movements, or LIDs, is one of the primary side effects of long-term L-DOPA therapy. Future research should look into whether group III mGlu agents cause undesirable dyskinetic effects similar to LIDs when administered alone, or if they can actually help reduce LIDs when given in combination with low-dose L-DOPA, as has recently

been observed with group I mGlu5 receptor antagonists in rodents [14,15]. Although it is currently too soon to determine whether group III mGlu receptor activation has any kind of long-term potential in the treatment of Parkinson's disease, the development of better systemically active medications that are more conducive to long-term administration to animals should make it possible for these problems to receive the proper care down the road. It will be clearer from future research whether receptor desensitization will affect the long-term usefulness of this strategy when focusing on group III mGlu receptors. Undoubtedly, a number of the responses mentioned above with the broad-spectrum agonists demonstrate that responses diminish at higher concentrations or doses tested [33,35,51]. These responses range from electrophysiological responses *in vitro* through to behavioral responses and neuroprotection *in vivo*. It has been demonstrated that the broad-spectrum agonist L-AP4 causes the fast internalization of at least two of the group III receptors, which could account for these data. mGlu4 and mGlu7 [61] mGlu receptors *in vitro*. The recent focus on creating mGlu4 receptor PAMs [18,62] may be explained by the likelihood that targeting the allosteric regions of receptors will lessen the likelihood that desensitization will become an issue. Research in the group III mGlu receptor field has not yet advanced to the point where the MPTP-treated primate serves as the last preclinical model for Parkinson's disease. The most therapeutically applicable model for tracking the long-term efficacy of treatments administered either by themselves or in conjunction with low-dose L-DOPA is this one. Therefore, research on MPTP-treated primates will shed light on the targeted group's potential for therapeutic applications. III mGlu receptors in Parkinson's disease (PD) and disclosing any unanticipated negative consequences that this tactic might have. Determining whether targeting group III mGlu receptors to achieve, among other things, such inhibition of glutamatergic transmission can occur without the occurrence of similar adverse effects will be crucial, since it is predicted that using ionotropic glutamate receptor antagonists to combat excessive glutamatergic transmission will result in unacceptable cognitive and psychomimetic adverse effects. While there is currently a dearth of information regarding group III mGlu agonists, recent clinical trials using agonists of the related class of group II (mGlu2 and mGlu3) receptors in patients with generalized anxiety disorder or schizophrenia have shown improvements in symptoms, good tolerance, and—most importantly-there have been no significant side effects from the treatment [63]. These early reports of targeting human group II mGlu receptors give hope that group III mGlu receptor-targeted medications may prove to be as well tolerated and free of undesired side effects, even though the results of longer-term clinical trials are still pending. The difficulty in creating "hit-to-lead" substances for group III mGlu receptors with tolerable systemic activity, nevertheless Potential benefit of focusing on group III mGlu receptors in Parkinson's disease. Finally, it is worthwhile to return our focus to the clinical setting. As stated in the Introduction, patients with Parkinson's disease (PD) experience a range of non-motor symptoms in addition to the basic motor symptoms, which further lowers their quality of life. Pain and melancholy are the most problematic of these. Thus, it is encouraging to learn that antidepressant effects in rats have been demonstrated by group III mGlu receptor activation after intraperitoneal injection (I.C.V.) administration of broad-spectrum agonists such as ACPT-I or the mGlu4 PAM PHCCC in combination with low-dose ACPT-I. The reports indicating intrathecal administration of ACPT-I, PHCCC, or systemic in inflammatory pain models, treatment of the mGlu8 agonist (S)-DCPG alleviated hyperalgesia [64], most likely by blocking glutamate release from

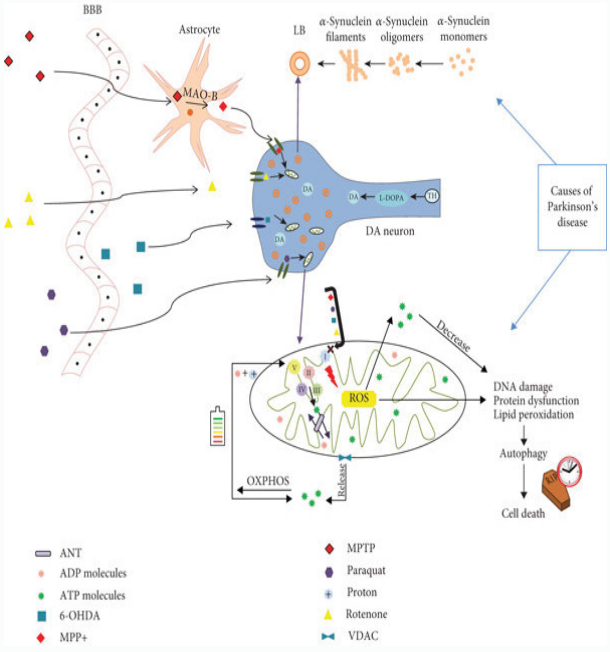

Figure 3: Parkinson's disease mechanism of action in the central nervous system and the pharmacokinetic effects of several agents that induce Parkinson-like symptoms. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) crosses the blood-brain barrier to be metabolized in 1-methyl-4-phenylpyridinium (MPP+) by monoamine oxidase B in the astrocytes. Afterwards, the transportation system of the synaptic cleft assists the intraneuronal MPP+ transfer and transports it further into the mitochondria where it impairs the mitochondrial respiration chain leading to reactive oxygen species production and dopaminergic neuron loss [38]. Similar to MPTP, paraquat could increase reactive oxygen species production, but in contrast to MPTP, it could lead to Lewy Body (LB) formation [39]. 6-Hydroxidopamine could also enter the dopaminergic neurons and lead to reactive oxygen species production in the absence of the Lewy body inclusions [15]. Following diffusion to intraneuronal space, rotenone inhibits mitochondrial complex I and promotes the formation of Lewy body inclusions [15,39]. Abbreviations: 6-OHDA-6-hydroxydopamine; ADP-adenosine diphosphate; ANT-adenine nucleotide translocase; ATP-adenosine triphosphate; BBB—blood-brain barrier; DA-dopamine; LB—- bodies; L-DOPA-levodopa; MAO-B-monoamine oxidase B; MPP-1-methyl-4-phenylpyridinium; MPTP—-1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; OXPHOS—oxidative phosphorylation; ROS—- oxygen species; TH—tyrosine; VDAC-voltage-dependent anion channel.

spinal cord primary afferents (Zhang et al., 2009). Lastly, it has been demonstrated that systemic injection of ACPT-I has antipsychotic effects in mice, and that activation of group III receptors, particularly mGlu7, inhibits glutamate release onto dopaminergic neurons in the ventral tegmental region [65]. Targeting group III mGlu receptors may offer a way to address some of the non-motor symptoms in Parkinson's disease (PD) in addition to addressing the motor symptoms and the ongoing destruction of dopaminergic neurons in the disease. prevent addiction-related behaviors or psychosis throughout treatment. These present promising opportunities for PD treatment-related drug discovery in the field of group III mGlu receptors.

Closing Thoughts

Ten years have passed since Bradley et al. [23] first showed positivity for group III mGlu receptors in the basal ganglia motor loop, and during that time, the possibility of using these receptors for therapeutic purposes has grown from theoretical to real. In rodent models of Parkinson's disease, activation of pre-synaptic group III mGlu receptors has been demonstrated to decrease transmission across

synapses in the indirect pathway (i.e., corticostriatal, striatopallidal, and subthalamic) [66-68]. This effect is most likely responsible for the reversal of symptoms observed after administration of agonist or PAMs of group III mGlu receptors. Activation of the Group III mGlu receptor has also been demonstrated to shield dopaminergic neurons against a variety of known poisons that cause dopaminergic reactions. Although the precise molecular processes behind these protective effects are yet unknown, it is likely that advantageous effects are achieved by activating group III mGlu receptors on both neurons and glia. In related fields, it has been demonstrated that activation of group III mGlu receptors produces actions (antidepressant, analgesic, and possibly anti-addictive) [69]. This suggests that, in addition to addressing the motor symptoms of Parkinson's disease (PD) and slowing down the progressive degeneration of dopaminergic neurons, targeting group III mGlu receptors may also help address some of the non-motor symptoms of the disease and prevent treatment-related addictive behaviors or psychosis. All of these findings present intriguing opportunities for the field of group III mGlu receptor drug discovery in the context of PD treatment [70-73]. Ventures should now focus on determining which particular group III mGlu receptors has the most promise (many studies have found that mGlu4 receptors are the most promising), figuring out the molecular mechanisms underlying neuroprotection, and targeting group III mGlu receptors in the MPTP-treated primate model of Parkinson's disease in order to determine the likely long-term therapeutic benefits of this approach.

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