Amino Acids (2002) 23: 185–191
DOI 10.1007/s00726-001-0127-1

Amino
Acids
Printed in Austria

Localization and physiological roles of metabotropic glutamate receptors in the direct and indirect pathways of the basal ganglia

M. J. Marino[1,2], **H. Awad**[1], **O. Poisik**[1], **M. Wittmann**[1], and **P. J. Conn**[1,2]

[1] Department of Pharmacology, Emory University School of Medicine, Atlanta, Georgia, U.S.A.
[2] Department of Neuroscience, Merck Research Laboratories, Merck and Co., Inc., West Point, Pennsylvania, U.S.A.

Received July 2, 2001
Accepted August, 6, 2001
Published online June 26, 2002

Summary. Our current understanding of the circuitry of the basal ganglia, and the pathophysiology of Parkinson's disease has led to major breakthroughs in the treatment of this debilitating movement disorder. Unfortunately, there are significant problems with the currently available pharmacological therapies that focus on dopamine replacement or dopaminergic agonists. Because of this, much effort has been focused on developing novel targets for the treatment of Parkinson's disease. The metabotropic glutamate receptors are a family of G-protein coupled receptors activated by glutamate. These receptors are differentially distributed throughout the basal ganglia in a manner suggesting that they may provide novel targets for the treatment of movement disorders. In this review we summarize anatomical and physiological data from our work and the work of other laboratories describing the distribution and physiological roles of metabotropic glutamate receptors in the basal ganglia with emphasis on possible therapeutic targets.

Keywords: Basal ganglia – Metabotropic glutamate receptors – Movement disorders – Parkinson's disease

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by disabling motor impairments including tremor, rigidity, and bradykinesia. The primary pathological change giving rise to the symptoms of Parkinson's disease is loss of dopaminergic neurons in the substantia nigra pars compacta that modulate the function of neurons in the striatum and other nuclei in the basal ganglia (BG) motor circuit (Fig. 1). Currently, the most effective pharmacological agents for treatment of PD include levodopa (L-DOPA), the immediate precursor of dopamine, and other drugs that replace the lost dopaminergic modulation of BG function (Poewe and Granata, 1997). Unfortunately, dopamine replacement therapy ultimately fails in most patients due to loss of efficacy with progression of the disease and severe motor and psychiatric side effects (Poewe et al., 1986). Because of this, a great deal of effort has been focused on developing new approaches for treatment of PD.

The primary input nucleus of the basal ganglia is the striatum (caudate, putamen, and nucleus accumbens), that receives dense innervation from the cortex and subcortical structures. The primary output nuclei of the basal ganglia are the substantia nigra pars reticulata (SNr) and the entopeduncular nucleus (EPN) which send GABAergic projections to the thalamus. The current model of cortical information flow through the basal ganglia states that the striatum projects to these output nuclei both directly, and indirectly through the globus pallidus and subthalamic nucleus (STN) (Albin et al., 1989; DeLong, 1990; Bergman et al., 1990). The direct pathway provides a GABAergic inhibition of the SNr/EPN, while the projection to globus pallidus relieves a GABAergic inhibition of STN, resulting in a glutamatergic excitation of SNr/EPN. A delicate balance between the inhibition of the output nuclei by the direct pathway, and excitation by the indirect pathway is believed to be crucial for control of movement, and any imbalance in this system underlies the pathophysiology of movement disorders.

Recent studies reveal that loss of nigrostriatal dopamine neurons results in a series of neurophysiological changes that lead to over activity of the indirect pathway, resulting in a pathological excitation of the STN. Increased activity of STN neurons leads to an

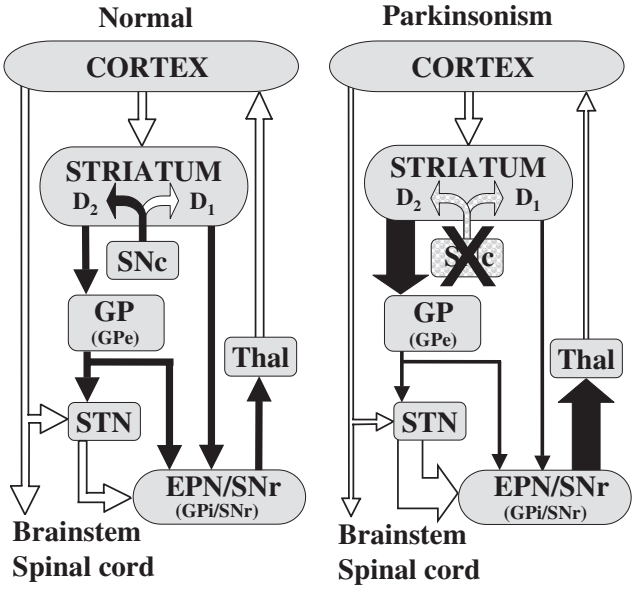

Fig. 1. The current model of how the Parkinson's-related loss of dopamine neurons in the SNc impacts information flow through the basal ganglia. Inhibitory connections are depicted by black arrows, excitatory transmission depicted by white arrows

increase in glutamate release at STN synapses onto GABAergic projection neurons in the output nuclei. This glutamate-mediated over excitation of BG output ultimately produces the motor impairment characteristic of PD (Wichmann and DeLong, 1997). Discovery of the pivotal role of increased activity in the indirect pathway in PD has led to a major focus on surgical approaches for treatment. For instance, lesions or high frequency stimulation of the STN provides a therapeutic benefit to PD patients (Limousin et al., 1995). In addition, pallidotomy, a surgical lesion of the GP, produces similar therapeutic effects by reversing the impact of increased activity of STN neurons (Laitinen et al., 1992; Baron et al., 1996). Development of these highly effective neurosurgical approaches provides a major advance in our understanding of the pathophysiology of Parkinson's disease. However, surgical approaches are not widely available to Parkinson's patients. Due to their invasive nature, high cost, and considerable expertise required, such treatment is reserved for patients that are refractory to dopamimetic therapy.

An alternative to surgical approaches to reducing the increased excitation of basal ganglia output nuclei in PD patients would be to employ pharmacological agents that counteract the effects of over activation of the STN neurons by reducing transmission through the indirect pathway. One approach would be to target metabotropic glutamate receptors (mGluRs). Eight mGluR subtypes have been cloned (designated mGluR1-mGluR8) from mammalian brain. These mGluRs are classified into three major groups based on sequence homologies, coupling to second messenger systems, and selectivities for various agonists (See Conn and Pin, 1997 for review). Group I mGluRs, which include mGluR1 and mGluR5, couple primarily to increases in phosphoinositide hydrolysis. Group II mGluRs (mGluR2 and mGluR3), and group III mGluRs (mGluR4, 6, 7, and 8) couple to inhibition of adenylyl cyclase. The mGluRs are widely distributed throughout the central nervous system and play important roles in regulating cell excitability and synaptic transmission (Conn and Pin, 1997; Anwyl, 1999). One of the primary functions of the mGluRs is a role as presynaptic receptors involved in reducing transmission at glutamatergic synapses. The mGluRs also serve as heteroreceptors involved in reducing GABA release at inhibitory synapses. Finally, postsynaptically localized mGluRs often play an important role in regulating neuronal excitability and in regulating currents through ionotropic glutamate receptors. If mGluRs play these roles in basal ganglia, particularly in the indirect pathway, members of this receptor family may provide an exciting new target for drugs that could be useful for the treatment of PD, as well as other disorders of BG function. In this chapter we will describe our current understanding of mGluR distribution and function in both the direct and the indirect pathway. Unless otherwise noted, all results presented are from studies of rat basal ganglia.

The striato-pallidal synapse

The indirect pathway arises from the striatal enkephalinergic medium aspiny neurons (Beckstead and Kersey, 1985; Gerfen and Young, III, 1988; Anderson and Reiner, 1990). These GABAergic neurons project to cells in the GP, forming the first synapses in the indirect pathway. Striatal neurons express mRNA for group I, II and III mGluRs (Testa et al., 1994). Of these, the group III mGluRs mGluR4 and mGluR7 have been localized to presynaptic striatopallidal terminals using both confocal and electron microscopy (Kosinski et al., 1999; Bradley et al., 1999a; Bradley et al., 1999b). Neurons in the GP express mRNA for mGluR1, 3, and 5 (Testa et al., 1994), and are immunoreactive for mGluR7 (Kosinski et al., 1999; Bradley et

al., 1999b). Postsynaptic localization has been demonstrated for mGluR1 (Testa et al., 1998), and mGluR7 (Kosinski et al., 1999; Bradley et al., 1999b) In addition, mGluR5 has been localized to postsynaptic sites at primate striatopallidal synapses (Hanson and Smith, 1999).

The model of the pathophysiology of PD outlined above states that the GABAergic projection neurons of the globus pallidus are inhibited in the parkinsonian state, leading to a disinhibition of the STN. However, recent findings have led to the speculation that a shift to burst firing in the GP may also play a role in PD (Chesselet and Delfs, 1996; Levy et al., 1997). Several recent functional studies have provided interesting insight into a potential role for the group I mGluRs in mediating firing frequency and burst firing in the GP. Activation of group I mGluRs induces direct effects on GP neurons including an inhibition of N or P-type calcium conductances (Stefani et al., 1994) and a direct depolarization which exhibits desensitization with repeated applications (Poisik et al., 2001). The pharmacology of this direct depolarization has been determined using the mGluR1-selective antagonist LY367385, and the mGluR5-selective antagonist MPEP. Interestingly, the DHPG-induced depolarization is completely blocked by preincubation with the mGluR1-selective antagonist indicating that mGluR1 is the sole mediator of this effect. However, blockade of mGluR5 with the selective antagonist MPEP produces a marked potentiation of the mGluR1-induced depolarization, blocks desensitization, and reveals a DHPG-induced oscillation in membrane potential.

The finding that mGluRs directly modulate GP neurons raises some interesting possibilities. While the primary input to the pallidum is GABAergic, there is some sparse glutamatergic input from the STN (Shink and Smith, 1995). Therefore, activation of the STN could directly excite pallidal neurons by actions on postsynaptic ionotropic and metabotropic glutamate receptors, and disinhibit pallidal neurons by actions on presynaptic mGluRs modulating GABA release. The resulting excitation of the GP would in turn inhibit the STN. This inhibitory feedback loop may play a role in regulating the balance of activity through the indirect pathway under normal conditions. However, in the case of PD, the sparse glutamatergic input may be insufficient to maintain this feedback control. The potential therapeutic value of restoring balance at this site will be determined by future studies on the role of group III mGluRs in modulating transmission at this synapse.

The pallido-subthalamic synapse

In contrast to the striatopallidal synapse, relatively little is known about the distribution of mGluRs at the pallidosubthalamic synapse. The projection neurons of the GP express mRNA for mGluR1, 3, and 5, and the glutamatergic projection neurons of the STN express mGluR1, 2, 3, and 5 mRNA (Testa et al., 1994). Recently, the group I mGluRs have been postsynaptically localized to dendrites of STN neurons at both symmetric and asymmetric synapses (Awad et al., 2000).

Activation of group I mGluRs induces a robust depolarization of STN neurons (Awad et al., 2000). Interestingly, this depolarization is blocked by the mGluR5-selective antagonist MPEP, but not by the mGluR1-selective antagonist CPCCOEt, indicating that only one of the group I mGluRs (mGluR5) localized at this synapse mediates the direct depolarization of these neurons. A role for the mGluR1 found at postsynaptic sites in the STN remains to be determined. In addition to directly depolarizing the STN neurons, group I mGluR activation also has been demonstrated to increase the frequency of STN burst firing (Beurrier et al., 1999; Awad et al., 2000). Since the switch from single spike activity to a burst-firing mode is one of the characteristics of parkinsonian states (Hollerman and Grace, 1992; Bergman et al., 1994; Hassani et al., 1996) this effect may play a key role in the neuropathology of this disease.

In addition to direct depolarizing effects, mGluR activation has been found to modulate synaptic transmission in the STN. Activation of the group I mGluR, mGluR1, or activation of the group III mGluRs induces a decrease in excitatory transmission through a presynaptic mechanism (Awad-Granko and Conn, 2001). In contrast to other regions in the BG, mGluRs do not appear to modulate inhibitory transmission in the STN (Awad-Granko and Conn, 2001).

The subthalamo-nigral synapse

Glutamatergic projections from the STN to the BG output nuclei constitute the final synapse in the indirect pathway. To date, the only study of mGluRs in the EPN has been an *in situ* study, and the results closely parallel findings in the SNr (Testa et al., 1994). Therefore, we

will focus on studies of the STN-SNr synapse. Neurons in the STN express mRNA for mGluR1, 2, 3, and 5, and the SNr GABAergic neurons express mRNA for mGluR1, 3, and 5 (Testa et al., 1994). Immunocytochemical studies have demonstrated presynaptic localization of mGluR2/3 (Bradley et al., 1999c), and 7 (Kosinski et al., 1999; Bradley et al., 1999b) at asymmetric synapses in the SNr. The presence of mGluR2 is of particular interest because it exhibits a rather restricted distribution in the BG. In addition to the STN, the only other BG cells found to express mGluR2 are the striatal cholinergic interneurons (Testa et al., 1994). Therefore, compounds selective for mGluR2 would be expected to exhibit relatively few side effects. The group I mGluRs have also been found postsynaptically localized at symmetric and asymmetric synapses in the SNr (Testa et al., 1998) (Hubert et al., 2001; Marino et al., 2001). Interestingly, subsynaptic localization of the group I mGluRs in SNr neurons has revealed an interesting pattern of localization. While both mGluR1 and mGluR5 are highly localized in these cells, only mGluR1 exhibits a high degree of membrane association (Hubert et al., 2001). As discussed below, this differential localization of these seemingly redundant receptor subtypes may have important functional consequences.

Several recent studies have provided a great deal of information on the physiological roles that mGluRs play in regulating the STN-SNr synapse. Activation of all three groups of mGluRs has been shown to inhibit glutamatergic transmission at this synapse (Bradley et al., 2000; Wittmann et al., 2001). In accord with the immunocytochemical studies, the pharmacology and physiology of this inhibition is consistent with actions on presynaptic group I mGluRs (mGluR1), group II mGluRs (mGluR2/3) and group III mGluRs (mGluR7). Activation of postsynaptic group I mGluRs produces a robust direct depolarization of SNr GABAergic neurons (Marino et al., 2001). This effect is blocked by the mGluR1-selective antagonist LY367385, but not by the mGluR5-selective MPEP. Therefore, in contrast to the effect of group I mGluR agonists in the STN, this effect appears to be mediated solely by mGluR1. Interestingly, stimulation of glutamatergic afferents in the SNr at frequencies consistent with the normal firing rate of STN neurons induces an mGluR-mediated slow EPSP which is completely blocked by LY367385 (Marino et al., 2001). This indicates that postsynaptic mGluR1 may play an important role in tonic regulation of basal ganglia output. The immunocytochemical findings that the majority of mGluR5 immunoreactivity is found in an intracellular compartment in neurons of the SNr (Hubert et al., 2001) provides a possible explanation as to why mGluR5 activation does not depolarize these cells. Furthermore, this raises the interesting possibility that some physiological or pathophysiological signal might alter mGluR5 localization or coupling and lead to a switch in the pharmacology, and possibly the magnitude of the group I-mediated response in SNr.

Since increased activity in the STN is believed to play a key role in the pathophysiology of PD (Wichmann and DeLong, 1997), the STN-SNr synapse is a logical site to target pharmacological interventions. Since the group II mGluRs are effective at decreasing transmission at this synapse, and exhibit a somewhat restricted distribution, these receptors could provide an ideal target for the development of antiparkinsonian compounds. Consistent with this, recent studies have demonstrated that systemic injection of the highly selective group II mGluR agonist LY354740 decreases haloperidol-induced muscle rigidity (Konieczny et al., 1998) and catalepsy (Bradley et al., 2000) in a rat model of PD. Furthermore, recent studies employing intranigral injections of the group II mGluR-selective agonist DCG-IV demonstrate a group II mGluR-specific reversal of reserpine-induced akinesia (Dawson et al., 2000) which suggest that the SNr is a likely site of action for these group II-mediated antiparkinsonian actions.

The direct pathway: the striato-nigral synapse

Approximately one half of the striatal medium aspiny neurons project directly to the basal ganglia output structures. As discussed above, relatively little is known about the role of mGluRs in the EPN, therefore, we will focus on the striato-nigral synapse. The general expression pattern and anatomical distribution of mGluRs in the striatum and SNr have been outlined in the previous sections. Specific presynaptic localization of the group III mGluR, mGluR7, to inhibitory terminals in the SNr has recently been described (Kosinski et al., 1999). Furthermore, lesion studies have verified that this labeling is localized to inhibitory terminals of striatal origin (Kosinski et al., 1999). In addition, both group I mGluRs are found localized to small unmyelinated axons and in axon terminals at symmetric synapses (Marino et al., 2001).

Consistent with the anatomical distribution, functional studies have found that activation of group I (Marino et al., 2001) or group III mGluRs (Wittmann et al., 2001) reduces inhibitory transmission in the SNr through a presynaptic mechanism of action. These results must be interpreted with caution due to the fact that it was not possible to distinguish between striatonigral and pallido-nigral projections in the *in vitro* slice preparation. While, a substantial proportion of inhibitory terminals onto SNr projection neurons arise from the striatum (Smith et al., 1998), effects on pallidonigral projections can not be ruled out. However, several important points can be made regarding the physiological roles mGluRs play in modulating inhibitory transmission in the SNr. While immunocytochemical studies indicate that the mGluR7 subtype is presynaptically localized at both striato-pallidal and striato-nigral synapses, mGluR4 is more abundant at striato-pallidal synapses (Kosinski et al., 1999; Bradley et al., 1999a, b). This suggests that mGluR7 may be positioned to modulate both the direct and indirect pathways, while mGluR4 may have a function more selective for the indirect pathway. The findings that activation of group I mGluRs induces a disinhibition of SNr GABAergic neurons is particularly interesting in light of the findings discussed above that demonstrate that activation of the group I, mGluR1, induces a robust depolarization of SNr neurons. Taken together, these findings suggest that in a Parkinsonian state excessive glutamate release from subthalamic terminals will act on mGluRs in the SNr to induce both a direct excitation of SNr output neurons, as well as an indirect disinhibition due to decreased GABAergic transmission. Therefore, mGluR activation in the SNr may help explain how the relatively sparse glutamatergic input from the STN can exert such a powerful excitatory drive in the Parkinsonian state.

Metabotropic glutamate receptors in other basal ganglia regions

While this review has focused on the direct and indirect pathway, it should be noted that mGluRs are expressed throughout the BG and have functional relevance at multiple sites. For example, input to the BG at the corticostriatal synapse is modulated both presynaptically by group II and III mGluRs and postsynaptically by group I mGluRs (East et al., 1995; Lovinger and McCool, 1995; Pisani et al., 1997). The main effect of the presynaptic mGluRs is to reduce the cortical input to the striatum (East et al., 1995; Lovinger and McCool, 1995; Pisani et al., 1997). Activation of the group I mGluRs produce a direct excitation of the indirect pathway as measured behaviorally, or by employing metabolic markers (Kaatz and Albin, 1995; Kearney et al., 1997). Interestingly, this effect appears to be mediated by dopamine, as it is blocked by acute dopamine depletion (Saccan et al., 1992; Kearney et al., 1998). However, chronic dopamine depletion does not block this effect (Kearney et al., 1998) suggesting that some compensatory mechanism exists in this system.

All three groups of mGluRs have been shown to modulate glutamatergic transmission in the substantia nigra pars compacta (Wigmore and Lacey, 1998). This finding is of particular interest since glutamate release in the SNc is hypothesized to play a role in the degeneration of the nigrostriatal dopamine system. While the source of the excitatory afferents regulated by mGluRs in SNc was not defined in these studies, it is likely that these EPSCs are mediated in part by activity at STN terminals. These data raise the exciting possibility that group II mGluR agonists have potential not only for reducing the symptoms of established PD, but could also slow progression of PD. Future studies will be needed to clearly define the role of increased STN activity in contributing to progression of the disorder and to rigorously define the mGluR subtypes involved in regulating transmission at STN-SNc synapses.

In addition to presynaptic modulation of synaptic transmission, postsynaptic mGluRs mediate a biphasic modulatory response in the SNc. Direct activation of group I mGluRs depolarizes dopaminergic neurons (Mercuri et al., 1993; Shen and Johnson, 1997; Meltzer et al., 1997). However, activation of the group I mGluRs by synaptically released glutamate or brief application of agonists induces an inhibitory response in dopaminergic neurons (Fiorillo and Williams, 1998). This inhibitory effect is mediated by the activation of a calcium-dependent potassium conductance and rapidly desensitizes to reveal the group I mGluR-mediated depolarization. This raises the interesting possibility that the temporal nature of receptor activation might determine the physiological response in these neurons.

In summary, the mGluRs are expressed throughout the basal ganglia and selectively modulate synaptic transmission and cell excitability throughout the circuit (Table 1). Studies of this family of receptors not

Table 1. Summary of distribution and physiological effect of mGluRs in the indirect pathway. Group numbers are indicated for mGluRs detected at mRNA or protein level. See text for references

Presynaptic localization and effects			
Synapse	mRNA	Protein	Physiological effect
Striato-pallidal	1, 3, 4, 5	4a, 7a	?
Pallido-subthalamic	1, 3, 5	?	?
Subthalamo-nigral	1, 2, 3, 5	2/3, 4a, 7a	Decrease Glutamate Release
Striato-nigral	1, 3, 4, 5	7a, 1, 5	Decrease GABA Release
Postsynaptic localization and effects			
Synapse	mRNA	Protein	Physiological effect
Striato-pallidal	1, 3, 5	1, 5, 7a	Direct depolarization (1) Modulation of mGluR1 function (5) Inhibition of Ca++ current (1/5)
Pallido-subthalamic	1, 2, 3, 5	1, 5	Direct depolarization (5)
Subthalamo-nigral	1, 3, 5	1, 5	Direct depolarization (1)

only provides insight to BG function, but holds promise for the development of therapeutic compounds for the treatment of movement disorders.

References

Albin RL, Young AB, Penney JB (1989) The functional anatomy of basal ganglia disorders. Trends Neurosci 12: 366–375

Anderson KD, Reiner A (1990) Extensive co-occurrence of substance P and dynorphin in striatal projection neurons: an evolutionarily conserved feature of basal ganglia organization. J Comp Neurol 295: 339–369

Anwyl R (1999) Metabotropic glutamate receptors: electrophysiological properties and role in plasticity. Brain Res Brain Res Rev 29: 83–120

Awad-Granko H, Conn PJ (2001) Activation of group I and group III metabotropic glutamate receptors inhibits excitatory transmission in the rat subthalamic nucleus. Neuropharmacology 41: 32–41

Awad H, Hubert GW, Smith Y, Levey AI, Conn PJ (2000) Activation of metabotropic glutamate receptor 5 has direct excitatory effects and potentiates NMDA receptor currents in neurons of the subthalamic nucleus. J Neurosci 20: 7871–7879

Baron MS, Vitek JL, Bakay RA, Green J, Kaneoke Y, Hashimoto T, Turner RS, Woodard JL, Cole SA, McDonald WM, DeLong MR (1996) Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-year results of a pilot study. Ann Neurol 40: 355–366

Beckstead RM, Kersey KS (1985) Immunohistochemical demonstration of differential substance P-, met-enkephalin-, and glutamic-acid-decarboxylase-containing cell body and axon distributions in the corpus striatum of the cat. J Comp Neurol 232: 481–498

Benazzouz A, Gross C, Feger J, Limousin P, Gao DM, Krack P, Benabid AL (1996) Single unit recordings of subthalamic nucleus and pars reticulata of substantia nigra in akineto-rigid parkinsonism. Society For Neuroscience Abstracts 22, 91.18

Bergman H, Wichmann T, Karmon B, DeLong MR (1994) The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. J Neurophysiol 72: 507–520

Beurrier C, Congar P, Bioulac B, Hammond C (1999) Subthalamic nucleus neurons switch from single-spike activity to burst-firing mode. J Neurosci 19: 599–609

Bradley SR, Standaert DG, Rhodes KJ, Rees HD, Testa CM, Levey AI, Conn PJ (1999a) Immunohistochemical localization of subtype 4a metabotropic glutamate receptors in the rat and mouse basal ganglia. J Comp Neurol 407: 33–46

Bradley SR, Standaert DG, Levey AI, Conn PJ (1999b) Distribution of group III mGluRs in rat basal ganglia with subtype-specific antibodies. Ann NY Acad Sci 868: 531–534

Bradley SR, Marino MJ, Wittmann M, Rouse ST, Levey AI, Conn PJ (1999c) Physiological roles of presynaptically localized type 2, 3 and 7 metabotropic glutamate receptors in rat basal ganglia. Soc Neurosci Abs 25: 176.16

Bradley SR, Marino MJ, Wittmann M, Rouse ST, Awad H, Levey AI, Conn PJ (2000) Activation of Group II Metabotropic Glutamate Receptors Inhibits Synaptic Excitation of the Substantia Nigra Pars Reticulata. J Neurosci 20: 3085–3094

Chesselet MF, Delfs JM (1996) Basal ganglia and movement disorders: an update. Trends Neurosci 19: 417–422

Conn PJ, Pin JP (1997) Pharmacology and functions of metabotropic glutamate receptors. Annu Rev Pharmacol Toxicol 37: 205–237

Dawson L, Chadha A, Megalou M, Duty S (2000) The group II metabotropic glutamate receptor agonist, DCG-IV, alleviates akinesia following intranigral or intraventricular administration in the reserpine-treated rat. Br J Pharmacol 129: 541–546

DeLong MR (1990) Primate models of movement disorders of basal ganglia origin. Trends Neurosci 13: 281–285

East SJ, Hill MP, Brotchie JM (1995) Metabotropic glutamate receptor agonists inhibit endogenous glutamate release from rat striatal synaptosomes. Eur J Pharmacol 277: 117–121

Fiorillo CD, Williams JT (1998) Glutamate mediates an inhibitory postsynaptic potential in dopamine neurons. Nature 394: 78–82

Gerfen CR, Young WS, III (1988) Distribution of striatonigral and striatopallidal peptidergic neurons in both patch and matrix com-

partments: an in situ hybridization histochemistry and fluorescent retrograde tracing study. Brain Res 460: 161–167

Hanson, JE, Smith, Y (1999) Group I metabotropic glutamate receptors at GABAergic synapses in monkeys. J Neurosci 19: 6488–6496

Hassani OK, Mouroux M, Feger J (1996) Increased subthalamic neuronal activity after nigral dopaminergic lesion independent of disinhibition via the globus pallidus. Neuroscience 72: 105–115

Hollerman JR, Grace AA (1992) Subthalamic nucleus cell firing in the 6-OHDA-treated rat: basal activity and response to haloperidol. Brain Res 590: 291–299

Hubert GW, Paquet M, Smith Y (2001) Differential subcellular localization of mGluR1a and mGluR5 in the rat and monkey Substantia nigra. J Neurosci 21: 1838–1847

Kaatz KW, Albin RL (1995) Intrastriatal and intrasubthalamic stimulation of metabotropic glutamate receptors: a behavioral and Fos immunohistochemical study. Neuroscience 66: 55–65

Kearney JA, Frey KA, Albin RL (1997) Metabotropic glutamate agonist-induced rotation: a pharmacological, FOS immunohistochemical, and [14C]-2-deoxyglucose autoradiographic study. J Neurosci 17: 4415–4425

Kearney JA, Becker JB, Frey KA, Albin RL (1998) The role of nigrostriatal dopamine in metabotropic glutamate agonist-induced rotation. Neuroscience 87: 881–891

Konieczny J, Ossowska K, Wolfarth S, Pilc A (1998) LY354740, a group II metabotropic glutamate receptor agonist with potential antiparkinsonian properties in rats. Naunyn Schmiedebergs Arch Pharmacol 358: 500–502

Kosinski CM, Risso BS, Conn PJ, Levey AI, Landwehrmeyer GB, Penney JB, Jr., Young AB, Standaert DG (1999) Localization of metabotropic glutamate receptor 7 mRNA and mGluR7a protein in the rat basal ganglia. J Comp Neurol 415: 266–284

Laitinen LV, Bergenheim AT, Hariz MI (1992) Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. J Neurosurg 76: 53–61

Levy R, Hazrati LN, Herrero MT, Vila M, Hassani OK, Mouroux M, Ruberg M, Asensi H, Agid Y, Feger J, Obeso JA, Parent A, Hirsch EC (1997) Re-evaluation of the functional anatomy of the basal ganglia in normal and Parkinsonian states. Neuroscience 76: 335–343

Limousin P, Pollak P, Benazzouz A, Hoffmann D, Le Bas JF, Broussolle E, Perret JE, Benabid AL (1995) Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet 345: 91–95

Lovinger DM, McCool BA (1995) Metabotropic glutamate receptor-mediated presynaptic depression at corticostriatal synapses involves mGLuR2 or 3. J Neurophysiol 73: 1076–1083

Marino MJ, Wittman M, Bradley SR, Hubert GW, Smith Y, Conn PJ (2001) Activation of group I metabotropic glutamate receptors produces a direct excitation and disinhibition of GABAergic projection neurons in the Substantia nigra pars reticulata. J Neurosci 21: 7001–7012

Meltzer LT, Serpa KA, Christoffersen CL (1997) Metabotropic glutamate receptor-mediated inhibition and excitation of substantia nigra dopamine neurons. Synapse 26: 184–193

Mercuri NB, Stratta F, Calabresi P, Bonci A, Bernardi G (1993) Activation of metabotropic glutamate receptors induces an inward current in rat dopamine mesencephalic neurons. Neuroscience 56: 399–407

Pisani A, Calabresi P, Centonze D, Bernardi G (1997) Activation of group III metabotropic glutamate receptors depresses glutamatergic transmission at corticostriatal synapse. Neuropharmacology 36: 845–851

Poewe WH, Granata R (1997) Pharmacological treatment of Parkinson's disease. In: Watts RL (ed) Movement disorders: neurological principals and practice. McGraw-Hill, New York, pp 201–219

Poewe WH, Lees AJ, Stern GM (1986) Low-dose L-dopa therapy in Parkinson's disease: a 6-year follow-up study. Neurology 36: 1528–1530

Poisik O, Smith Y, Conn PJ (2001) Group I metabotropic glutamate receptors 1 and 5 have distinct functional roles in the rat Globus pallidus. Society For Neuroscience, Abstracts 31: 291.5

Saccan AI, Bymaster FP, Schoepp DD (1992) Metabotropic glutamate receptor activation produces extrapyramidal motor system activation that is mediated by striatal dopamine. J Neurochem 59: 245–251

Shen KZ, Johnson SW (1997) A slow excitatory postsynaptic current mediated by G-protein-coupled metabotropic glutamate receptors in rat ventral tegmental dopamine neurons. Eur J Neurosci 9: 48–54

Shink E, Smith Y (1995) Differential synaptic innervation of neurons in the internal and external segments of the globus pallidus by the. J Comp Neurol 358: 119–141

Smith Y, Bevan MD, Shink E, Bolam JP (1998) Microcircuitry of the direct and indirect pathways of the basal ganglia. Neuroscience 86: 353–387

Stefani A, Pisani A, Mercuri NB, Bernardi G, Calabresi P (1994) Activation of metabotropic glutamate receptors inhibits calcium currents and GABA-mediated synaptic potentials in striatal neurons. J Neurosci 14: 6734–6743

Testa CM, Friberg IK, Weiss SW, Standaert DG (1998) Immunohistochemical localization of metabotropic glutamate receptors mGluR1a and mGluR2/3 in the rat basal ganglia. J Comp Neurol 390: 5–19

Testa CM, Standaert DG, Young AB, Penney JB, Jr. (1994) Metabotropic glutamate receptor mRNA expression in the basal ganglia of the rat. J Neurosci 14: 3005–3018

Testa CM, Standaert DG, Landwehrmeyer GB, Penney JB, Jr., Young AB (1995) Differential expression of mGluR5 metabotropic glutamate receptor mRNA by rat striatal neurons. J Comp Neurol 354: 241–252

Wichmann T, DeLong MR (1997) Physiology of the basal ganglia and pathophysiology of movement disorders of basal ganglia origin. In: Watts RL (ed) Movement disorders: neurological principals and practice. McGraw-Hill, New York, pp 87–97

Wigmore MA, Lacey MG (1998) Metabotropic glutamate receptors depress glutamate-mediated synaptic input to rat midbrain dopamine neurones in vitro. Br J Pharmacol 123: 667–674

Wittmann M, Marino MJ, Bradley SR, Conn PJ (2001) Activation of group III mGluRs inhibits GABAergic and glutamatergic transmission in the Substantia nigra pars reticulata. J Neurophysiol 85: 1960–1968

Authors' address: Dr. P. Jeffrey Conn, Merck and Company, Inc., 770 Sumneytown Pike, PO Box 4, WP46-300, West Point, PA 19486-0004 U.S.A., Fax: (215) 652-3811, E-mail: jeff_conn@merck.com