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Striatal metabotropic glutamate receptors as a target for pharmacotherapy in Parkinson's disease

Review Article

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Summary. Parkinson's disease (PD) is a common neurodegenerative disorder characterized by the loss of dopamine (DA)-containing neurons in the substantia nigra pars compacta (SNc). The symptoms are resting tremor, slowness of movement, rigidity and postural instability. Evidence that an imbalance between dopaminergic and cholinergic transmission takes place within the striatum led to the utilization of DA precursors, DA receptor agonists and anticholinergic drugs in the symptomatic therapy of PD. However, upon disease progression the therapy becomes less effective and debilitating effects such as dyskinesias and motor fluctuations appear. Hence, the need for the development of alternative therapeutic strategies has emerged.

Several observations in different experimental models of PD suggest that blockade of excitatory amino acid transmission exerts antiparkinsonian effects. In particular, recent studies have focused on metabotropic glutamate receptors (mGluRs). Drugs acting on group I and II mGluRs have indeed been proven useful in ameliorating the parkinsonian symptoms in animal models of PD and therefore might represent promising therapeutic targets. This beneficial effect could be due to the reduction of both glutamatergic and cholinergic transmission. A novel target for drugs acting on mGluRs in PD therapy might be represented by striatal cholinergic interneurons. Indeed, the activation of mGluR2, highly expressed on this cell type, is able to reduce calcium-dependent plateau potentials by interfering with somatodendritic N-type calcium channel activity, in turn reducing ACh release in the striatum. Similarly, the blockade of both group I mGluR subtypes reduces cholinergic interneuron excitability, and decreases striatal ACh release. Thus, targeting mGluRs located onto cholinergic interneurons might result in a beneficial pharmacological effect in the parkinsonian state.

Keywords: Metabotropic glutamate receptors – Striatum – Parkinson's disease – Cholinergic interneurons

Introduction

Parkinson's disease (PD) is a severe neurodegenerative disorder mainly affecting the substantia nigra pars compacta (SNc) (Wichmann and DeLong, 2003). The resultant denervation of dopaminergic terminals within the basal ganglia is the functional substrate for motor symptoms of PD, such as bradykinesia, tremor and rigidity.

The striatum, the input nucleus of the basal ganglia circuit, is the main recipient of nigral dopaminergic fibers. Moreover, beyond receiving a massive glutamatergic input from both the cortex and the thalamus, this is also the brain structure showing the highest acetylcholine (ACh) content. This strong convergence of dopaminergic and cholinergic constituents enables close interactions. Indeed ACh and dopamine (DA) work in concert, and loss of this cooperative activity contributes to the dysfunction underlying PD. This hypothesis is supported by the observation that in PD the striatal ACh content is enhanced and in fact early pharmacotherapy of PD consisted in anticholinergic drugs (Duvoisin, 1967). On the other hand, undesirable side-effects have seriously limited the use of these drugs. To date, the current pharmacological approach to the therapy of parkinsonian symptoms relies on either DA replacement or DA agonists. However, the progressive development of intolerable motor adverse

effects after prolonged therapy, dyskinesias and motor fluctuations, prompted the search for new therapeutic approaches to PD.

Glutamatergic transmission in PD

DA-denervation induces a complex rearrangement within the basal ganglia circuitry and profound modifications in the activity of the glutamatergic pathways (Wichmann and DeLong, 2003). The glutamatergic neurotransmission in the basal ganglia is driven by cortical projections to the striatum, the subthalamic nucleus (STN) and the SNc, by the thalamic projections, and by the STN afferents to the internal globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). In PD the excitability of thalamic neurons has been shown to be reduced, and the firing pattern altered (Ceballos-Bauman et al., 1994; Vitek et al., 1994). These alterations in the thalamic activity are due to an increased GABAergic activity deriving from the output nuclei of the basal ganglia, GPi and SNr. Conversely, the glutamatergic activity of both the subthalamic projection neurons and the corticostriatal pathway is dramatically increased. Therapeutic approaches aiming at the reduction of the STN overactivity, either by functional inactivation through deep brain stimulation or by surgical ablation, proved useful in PD patients (Bergman et al., 1990). In an animal model of PD, focal infusion of NMDA receptor antagonists was able to prevent nigral degeneration, suggesting that the subthalamic projections to the substantia nigra might promote excitotoxic damage to dopaminergic neurons (Blandini et al., 2001). In addition, in PD the firing of subthalamic neurons has been reported to be shifted from an irregular pattern to a synchronized, oscillatory activity that might recruit the output targets, thus resulting in an abnormal coding of motor processes (Bevan et al., 2002). The increased activity of the corticostriatal synaptic transmission after DA-denervation is likely to play a key role in the pathophysiology of PD. In a rodent model of PD an enhancement of glutamate-mediated spontaneous and evoked postsynaptic potentials has been reported (Calabresi et al., 2000; Picconi et al., 2002). In this model, STN lesion has been recently reported to revert both the abnormalities in motor behaviour and the enhancement in striatal glutamatergic synaptic transmission (Centonze et al., 2005). Accordingly, focal administration of NMDA receptor antagonists into the striatum exerts antiparkinsonian effects in experimental models of PD (Hallett and Standaert, 2004). However, clinical trials utilizing NMDA receptor antagonists in humans has been limited because of the severe cognitive and psychomimetic adverse effects due to the non-selective receptor blockade (Parsons et al., 1998; Chase and Oh, 2000; Hallett and Standaert, 2004).

Metabotropic glutamate receptors

The failure of pharmacological approaches targeting NMDA receptors in PD therapy prompted much interest on metabotropic glutamate receptors (mGluRs) as novel candidates (Rouse et al., 2000; Bruno et al., 2001; Ossowska et al., 2002; Marino and Conn, 2002; Feeley Kearney and Albin, 2003; Gubellini et al., 2004). Several studies have shown that the pharmacological modulation of mGluRs can ameliorate motor abnormalities in experimental models of PD. In particular, group II mGluR agonists have been shown to reduce both reserpine-induced akinesia and muscle rigidity caused by haloperidol treatment in rats (Konieczny et al., 1998; Dawson et al., 2000; Murray et al., 2002). More recently, the group II mGluR agonist LY379268 has been reported to exert a neuroprotective effect in the MPTP-treated mice, as measured by the reduction in the extent of nigro-striatal degeneration (Battaglia et al., 2003). In addition to agonists at group II mGluRs, recently also agonists acting at group III mGluRs have been reported to exert anti-akinetic effects in reserpine-treated rats (MacInnes et al., 2004). As an alternative to group II or III mGluR activation, inhibition of group I mGluRs (mGluR1 and mGluR5) seems promising in PD therapy. Indeed, blockade of mGluR5 was shown to alleviate akinesia in both 6-OHDA and haloperidol-treated animals (Spooren et al., 2001; Ossowska et al., 2001; Breysse et al., 2002). In addition, a recent study showed that mGluR5 knockout mice are less sensitive to MPTP toxicity, and that mGluR5 antagonists are effective in reducing the MPTP-induced nigrostriatal damage in wild-type mice (Battaglia et al., 2004).

The mechanism by which the modulation of mGluR activity exerts beneficial effects in animal models of PD still has to be elucidated. Activation of either group II or III mGluRs has been shown to reduce corticostriatal glutamatergic transmission (Pisani et al., 1997, 2000). Interestingly, an enhanced sensitivity to group II and possibly group III receptor stimulation has been reported to occur in the striatum of 6-OHDA-lesioned rats (Picconi et al., 2002; Feely Kearney and Albin, 2003). This might represent a compensatory mechanism intervening to reduce the corticostriatal glutamatergic overactivity induced by DA denervation.

Though the hyperactivity of corticostriatal transmission has a central role in the pathophysiology of PD, mGluRs

are widely expressed in the basal ganglia, thus pharmacological agents aimed at modulating their activity could indeed act at many levels. Accordingly, the beneficial effects observed in animal models of PD after systemic administration of group II mGluR agonists could derive from the reduction of both corticostriatal transmission and STN hyperactivity (Rouse et al., 2000; Murray et al., 2002). Moreover, the anti-akinetic effect of group III mGluR agonists on reserpine-treated rats has been observed after injection into the output nuclei of the basal ganglia, GPi and SNr (MacInnes et al., 2004). Several authors point out that the beneficial effects of group I mGluRs might be due to the normalization of the glutamatergic transmission at many levels in the basal ganglia circuitry: striatum, STN, SNr and GPi (Ossowska et al., 2002; Feeley Kearney and Albin, 2003; Gubellini et al., 2004). Besides, it must be noted that the expression of mGluRs is not homogeneous even among the different neuronal subtypes within the same basal ganglia structure.

Expression and role of striatal mGluRs

Group I, II, III mGluRs have been reported to be expressed in the striatum. Group I mGluRs (mGluR1 and 5) have a postsynaptic localization on striatal neurons, whereas group II (mGluR2 and 3) and group III (mainly mGluR7) have been described at presynaptic level on excitatory corticostriatal terminals and GABAergic output fibers (Testa et al., 1995, 1998; Tallaksen-Greene et al., 2003; Kosinski et al., 1999; Smith et al., 2000; Corti et al., 2002; Pisani et al., 2001a, 2002). The main population of striatal neurons, represented by medium spiny GABAergic projection neurons, has been reported to express both mGluR1 and 5 (Kerner et al., 1997; Smith et al., 2000). Either the group I mGluR agonist 3,5-dihydroxyphenilglycine (3,5-DHPG) or the selective mGluR5 agonist (*RS*)-2-chloro-5-hydroxyphenylglycine (CHPG) causes an enhancement of the cationic currents gated by NMDA receptors, without affecting the membrane properties. The observation that the potentiation of NMDA-induced response is not observed in mice lacking mGluR5, while it is preserved in mice lacking mGluR1, further strengthen the hypothesis that this action is mediated by the mGluR5 subtype (Pisani et al., 2001b). In addition, group I mGluRs have been shown to be selectively involved in corticostriatal synaptic plasticity. In particular, activation of mGluR1 is required for the induction of corticostriatal long term depression (LTD), as shown by pharmacologic blockade or genetic ablation of this receptor subtype (Conquet et al., 1994; Gubellini et al., 2001; Sung et al., 2001). The role of group I mGluRs in LTD probably resides in their ability to increase the intracellular calcium level, a key regulator in the induction of striatal synaptic plasticity (Bonsi et al., 2003). The induction of the opposite form of corticostriatal synaptic plasticity, long term potentiation (LTP), requires both group I mGluR subtypes. Recent data show that blockade of either mGluR1 or mGluR5 partially reduces the amplitude of LTP, without preventing it, and only the simultaneous blockade of both receptors is able to block the induction of corticostriatal LTP (Gubellini et al., 2003). Accordingly, corticostriatal LTP is reduced both in mGluR1$-/-$ and mGluR5$-/-$ mice, where it can be prevented by the administration of a mGluR5 or mGluR1 antagonist, respectively (Conquet et al., 1994; Chiamulera et al., 2001).

Activation of either group II or III mGluRs by the selective agonists causes the inhibition of excitatory corticostriatal synaptic transmission in medium spiny neurons through pre-synaptic mechanisms, without affecting the membrane properties (Calabresi et al., 1992; Lovinger and McCool, 1995; Pisani et al., 1997, 2000).

Thus, blockade of group I or activation of group II and III mGluRs can exert beneficial effects in PD by acting at many levels in the striatum to reduce glutamatergic neurotransmission.

An additional neuroprotective mechanism involving striatal mGluRs could be represented by the activation of group II mGluRs on glial cells. Indeed, group II mGluR agonists enhance the production and release of glial transforming growth factor-β, that has been reported to exert a neuroprotective effect in mixed cortical cultures challenged with NMDA (Bruno et al., 1998).

Striatal cholinergic interneurons

The hypothesis of an imbalance between DA and ACh in parkinsonian striatum, leading to pharmacotherapy based on anticholinergic drugs, emphasises the role of striatal cholinergic interneurons in the pathophysiology of PD (Duvoisin, 1967). These neurons represent a small percentage of the striatal neuronal population, though they provide the striatum with the highest ACh content in the brain, and have been identified as the tonically active neurons (TANs) that during in vivo recordings from the primate striatum respond to rewarding stimuli (Graybiel et al., 1994). DA denervation following MPTP treatment in monkeys causes the loss of the TAN conditioned response (Aosaki et al., 1994). Interestingly, after MPTP treatment, TANs and pallidal neurons acquire a synchro-

nous firing activity, showing a frequency resembling the PD tremor range (Raz et al., 2001). Hence, it has been suggested that, due to the abundant expression of mGluRs on these cells, modulation of the activity of these receptors might represent an additional target in PD therapy. Striatal cholinergic interneurons express group I mGluR1 and 5, and group II receptors (Testa et al., 1995, 1998; Tallaksen-Greene et al., 2003; Pisani et al., 2002; Bell et al., 2002). Recent in situ hybridization experiments have revealed the expression of mGluR2, but not mGluR3, by large cholinergic interneurons (Pisani et al., 2002). Activation of mGluR2 has been shown to inhibit the excitability of this cells both by depressing excitatory synaptic inputs and by direct inhibition of postsynaptic P-type calcium conductance, thus in turn reducing ACh release (Figs. 1, 2) (Pisani et al., 2002). Group II mGluR agonists, DCGIV and LY379268, were shown to depress the amplitude of the pharmacologically isolated corticostriatal glutamatergic component of the postsynaptic potential, evoked by synaptic stimulation in rat brain slices (Fig. 1A). Moreover, LY379268 reduced the duration of spontaneous plateau-potentials, an experimental paradigm of cell excitability, and the amplitude of concomitant calcium transients (Fig. 1B). This effect was mediated by inhibition of P-type calcium channels, as it was mimicked and occluded by the selective channel blocker ω-agatoxin-IVA. Further evidence of the inhibitory action of group II mGluR activation on the excitability of cholinergic interneurons was provided by the direct measurement of the level of striatal ACh. Accordingly, both the group II mGluR agonists DCGIV or LY379268 and the P-type calcium channel blocker ω-agatoxin-IVA reduce the striatal ACh release induced by electrical stimulation (Pisani

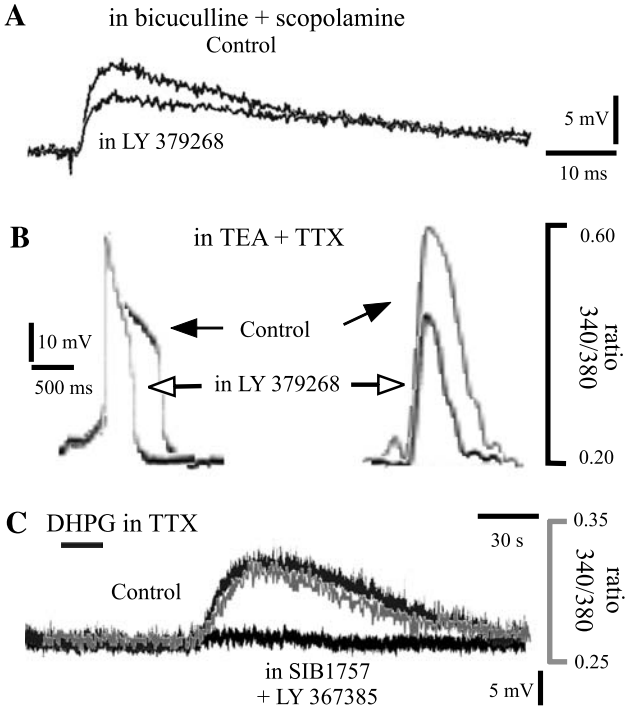

Fig. 1. Electrophysiological effects of mGluR subtype activation on striatal cholinergic interneurons recorded from corticostriatal slices. **A** The glutamate-mediated component of the postsynaptic potential evoked by synaptic stimulation is pharmacologically isolated by perfusion of the slice with bicuculline and scopolamine, to block the GABAergic and muscarinic components, respectively. The group II mGluR agonist LY379268 reversibly reduces the amplitude of the excitatory postsynaptic potential in cholinergic interneurons. **B** During recordings with electrodes filled with cesium, perfusion of the slices with tetraethylammonium (TEA) and tetrodotoxin (TTX) induces the appearance of long-lasting depolarizations, plateau-potentials (left), coupled to large calcium transients (right), in the recorded cholinergic interneuron. The intracellular calcium level is measured by the ratio in the 340 vs 380 nm fluorescence of the selective dye bis-fura-2. The selective group II mGluR agonist, LY379268, reduces the duration of plateau-potentials and the amplitude of calcium transients. **C** During intracellular recordings from rat slices, activation of group I mGluRs by perfusion with the selective agonist 3,5-DHPG causes a depolarization coupled to an increase of the intracellular calcium level in cholinergic interneurons. Only co-administration of mGluR1 and 5 antagonists, respectively LY367385 and SIB1757, blocks the 3,5-DHPG-induced depolarizing response

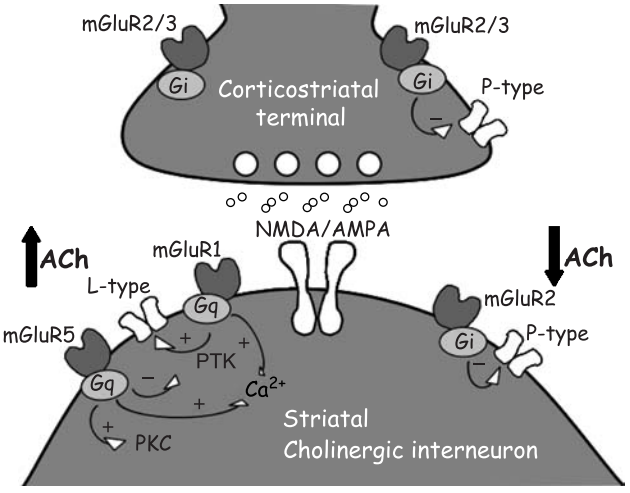

Fig. 2. Simplified scheme reporting the effects of pre- and postsynaptic mGluR activation on striatal ACh content. Activation of group I mGluR subtypes, mGluR1 and 5, increases the excitability and intracellular calcium (Ca^{2+}) level in cholinergic interneurons, therefore, in turn, the striatal ACh content. Complex interactions take place between mGluR1 and 5. Selective activation of tyrosine kinase (PTK) by mGluR1, or protein kinase C (PKC) by mGluR5 differently contributes to shape cell and network activity by regulating low-frequency membrane potential oscillations and receptor desensitization, respectively. Group II mGluRs act both at pre- and postsynaptic level to reduce the excitability of cholinergic interneurons and ACh release. Activation of group II mGluRs located on corticostriatal terminals, by inhibiting P-type calcium channels, reduces glutamate-mediated excitatory postsynaptic potentials. In addition, postsynaptic mGluR2 directly reduces the cell excitability by acting on P-type calcium channels

et al., 2002). In addition, group I mGluR antagonists reduce the ACh release (Marti et al., 2001). In cholinergic interneurons activation of either group I mGluR1 or 5 subtype induces a membrane depolarization/inward current coupled with an increase of both membrane resistance and intracellular calcium levels (Fig. 1C) (Takeshita et al., 1996; Pisani et al., 2001a; Bell et al., 2002; Bonsi et al., 2005). The reversal of the group I mGluR-induced current indicates that it is mainly mediated by a K^+ conductance (Takeshita et al., 1996; Bonsi et al., 2005). This apparently redundant role is a peculiar feature of this class of interneurons, as in other neuronal populations of the basal ganglia distinct physiological roles for mGluR1 and 5 have been reported (Awad et al., 2000; Pisani et al., 2001b; Valenti et al., 2002; Poisik et al., 2003). Recent data strongly suggest that complex interactions occur between group I mGluR subtypes in striatal cholinergic interneurons, ultimately modulating cell excitability, ACh content, and neuronal network activity. Repeated or prolonged group I mGluR stimulation was shown to induce a progressive decline in the amplitude of the cell response, suggesting a desensitization of the receptor (Bonsi et al., 2005). Interestingly, the receptor desensitization was not observed after blockade of mGluR5, whereas it still occurred in LY367385, a selective mGluR1 antagonist. These observations suggest the occurrence of a homologous desensitization of mGluR5, though a mGluR5-mediated desensitization of mGluR1, as described in type II neurons of the globus pallidus, can not be ruled out (Poisik et al., 2003). MGluR desensitization to glutamatergic input in cholinergic interneurons, by tuning striatal ACh levels, might represent a possible target for therapeutic strategies aimed at limiting ACh overflow in PD (Calabresi et al., 2000; Pisani et al., 2003).

In a percentage of cholinergic interneurons, after blockade of mGluR5, group I mGluR agonist induces an oscillatory response of the membrane potential (Bonsi et al., 2005). It has been suggested that mGluR5 might exert a tonic inhibitory action on the transduction pathway of mGluR1. During prolonged exposure to endogenous glutamate, as in case of sustained synaptic activation, the desensitization of the receptor releases this inhibitory control, thus disclosing the mGluR1-mediated membrane potential oscillations. Interestingly, these oscillations closely resemble the rhythmic activity, sustained by a K^+ conductance, recently observed in a subgroup of striatal cholinergic interneurons (Wilson, 2005).

In conclusion, both antagonists at group I mGluRs and agonists at mGluR2 can be beneficial in PD also by acting on cholinergic interneurons and reducing striatal ACh. In addition, the complex interactions occurring between mGluR1 and 5 to shape the excitability of cholinergic interneurons, could represent a novel target for therapeutic strategy in PD.

Conclusions

L-DOPA and dopaminergic agonists represent the current symptomatic pharmacotherapy for PD. However, treatment with either DA precursors or DA receptor agonists is not devoid of serious side effects such as dyskinesias and motor fluctuations. Evidence of an increased glutamatergic transmission in PD led several investigators to test drugs counteracting the effects of glutamate as a novel neuroprotective and symptomatic approach to PD therapy. Ionotropic glutamate receptors, in particular NMDA receptors, have represented a target for pharmacological research in PD (Parsons et al., 1998; Chase and Oh, 2000; Hallett and Standaert, 2004). Beside reducing the occurrence of parkinsonian symptoms, unfortunately NMDA receptor antagonists also produce undesirable side effects, hallucinations and cognitive deficits, and have therefore been excluded from PD therapy. The most recent research on glutamatergic transmission in PD suggests that mGluRs represent promising therapeutic target for different pathological conditions, including PD (Rouse et al., 2000; Bruno et al., 2001; Ossowska et al., 2002; Marino and Conn, 2002; Feeley Kearney and Albin, 2003; Pisani et al., 2003; Gubellini et al., 2004). Yet, further work is needed, in order to identify at cell level the site within the basal ganglia circuitry where mGluR drugs act to exert their beneficial effect in PD.

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