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Metabotropic glutamate receptors: targets for neuroprotective therapies in Parkinson disease

Gunasingh J Masilamoni[1,3] and Yoland Smith[1,2,3]

Metabotropic glutamate receptors (mGluRs) are heavily expressed throughout the basal ganglia (BG), where they modulate neuronal excitability, transmitter release and long term synaptic plasticity. Therefore, targeting specific mGluR subtypes by means of selective drugs could be a possible strategy for restoring normal synaptic function and neuronal activity of the BG in Parkinson disease (PD). Preclinical studies have revealed that specific mGluR subtypes mediate significant neuroprotective effects that reduce toxin-induced midbrain dopaminergic neuronal death in animal models of PD. Although the underlying mechanisms of these effects must be further studied, there is evidence that intracellular calcium regulation, anti-inflammatory effects, and glutamatergic network modulation contribute to some of these neuroprotective properties. It is noteworthy that these protective effects extend beyond midbrain dopaminergic neurons to include other monoam
inergic cell groups for some mGluRs. In this review, we discuss evidence for mGluR-mediated neuroprotection in PD and highlight the challenges to translate these findings into human trials.

Addresses
[1] Yerkes National Primate Research Center, Emory University, 954, Gatewood Rd NE, Atlanta, GA 30322, USA
[2] Department of Neurology, Emory University, 954, Gatewood Rd NE, Atlanta, GA 30322, USA
[3] Udall Center of Excellence for Parkinson's Disease, Emory University, 954, Gatewood Rd NE, Atlanta, GA 30322, USA

Corresponding author: Smith, Yoland (ysmit01@emory.edu)

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Introduction

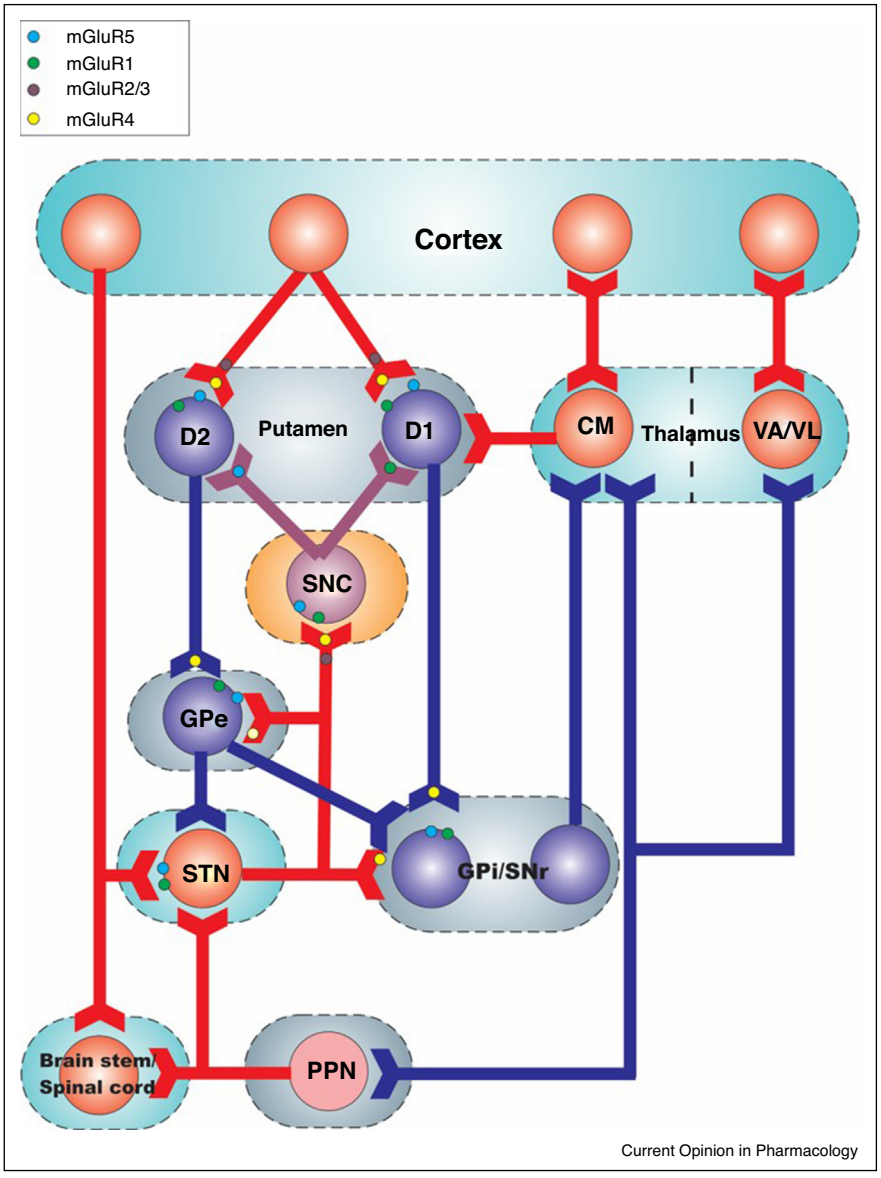
Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder clinically characterized by motor disturbances such as resting tremor, slowness of movement (bradykinesia), difficulty in initiating movements (akinesia), rigidity and postural instability. The motor symptoms largely arise through the progressive degeneration of dopamine (DA) neurons in the substantia nigra pars compacta (SNC). These DA neurons are a key component of the basal ganglia (BG), a highly organized network of brain nuclei implicated in motor, limbic and cognitive functions that receive massive extrinsic glutamatergic projections from the cortex and thalamus (Figure 1). The onset of parkinsonian motor symptoms appears only after a critical threshold of 50–60% DA neurons loss in SNC and 70–80% degeneration of striatal DA terminals has been reached [1]. This lag between the development of motor deficits and the protracted extent of the nigrostriatal degenerative process provides an opportunity for neuroprotective intervention that could slow down the degeneration of the DA system, thereby delay or prevent the development of parkinsonian motor symptoms.

It is well recognized that PD symptoms extend beyond motor deficits, and include cognitive, psychiatric and autonomic dysfunctions. These non-motor signs are increasingly recognized as being part of the wider clinical syndrome of PD and a major source of decreased quality of life for PD patients [2]. There is compelling evidence that some of these non-motor deficits result from the degeneration of noradrenergic neurons in the locus coeruleus (LC) and adjoining areas, a pathological feature described in the postmortem brain of PD patients [3••,4]. To date, the most effective treatment for parkinsonian motor symptoms relies on DA replacement therapy. However, as the disease advances, there is an emergence of complications related to long-term symptomatic treatment, including motor and non-motor fluctuations, dyskinesia, and psychosis [5]. Thus, there is an urgent need to develop therapies that slow down the progression of neurodegeneration in PD.

The development of therapeutic approaches that could slow down the death of midbrain DAergic neurons has been of great interest during the past decades. Although there is preclinical evidence that blockade of AMPA and NMDA ionotropic glutamate receptors protects midbrain dopaminergic neurons from toxin-induced degeneration in rodent and monkey models of PD [6], chronic administration of ionotropic glutamate receptor antagonists elicits unwanted side effects in humans, thereby limiting their usefulness as therapeutics [6].

Because of their modulatory effects, localization specificity and potential for drug targeting at allosteric

Figure 1



Localization of metabotropic glutamate receptors (mGluR) subtypes in the basal ganglia motor circuit. Eight mGluR subtypes (mGluR1–mGluR8) have been cloned and divided into three groups (Groups I–III). Group I mGluRs (mGluR1 and 5) are predominantly expressed postsynaptically in dendrites and spines. Presynaptic expression in nigrostriatal dopamine terminals has also been reported in the primate striatum. Group II (mGluRs 2 and 3) and group III (mGluRs 4, 6, 7 and 8) are mainly localized presynaptically in glutamatergic and non-glutamatergic terminals, where they act as auto-receptors or hetero-receptors that reduce neurotransmitter release. The blockade of group I receptors and activation of groups II and III mGluRs can reduce glutamatergic signalling and dampen neuronal excitability giving them potential neuroprotective properties.

modulatory sites, the G protein-coupled metabotropic glutamate receptors have generated significant interest as new therapeutic targets for brain diseases, including PD [6,7••].

In this review, we will discuss evidence for neuroprotective properties of different subtypes of mGluRs in PD and the challenges that need to be overcome to translate the findings of preclinical neuroprotection studies in animal models to the human diseased condition.

Anatomical localization and function of mGluRs in the basal ganglia circuitry

The mGluRs family comprises eight receptor subtypes classified into three groups: group I (mGluR1 and 5), group II (mGluR2 and 3), and group III (mGluR4, 6, 7 and