Functional Properties of AMPA and NMDA Receptors Expressed in Identified Types of Basal Ganglia Neurons

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AMPA- and NMDA-type glutamate receptors (AMPA and NMDARs) mediate excitatory synaptic transmission in the basal ganglia and may contribute to excitotoxic injury. We investigated the functional properties of AMPARs and NMDARs expressed by six main types of basal ganglia neurons in acute rat brain slices (principal neurons and cholinergic interneurons of striatum, GABAergic and dopaminergic neurons of substantia nigra, globus pallidus neurons, and subthalamic nucleus neurons) using fast application of glutamate to nucleated and outside-out membrane patches. AMPARs in different types of basal ganglia neurons were functionally distinct. Those expressed in striatal principal neurons exhibited the slowest gating (desensitization time constant $\tau = 11.5$ msec, 1 mM glutamate, 22°C), whereas those in striatal cholinergic interneurons showed the fastest gating (desensitization time constant $\tau = 3.6$ msec). The lowest Ca^{2+} permeability of AMPARs was observed in nigral dopaminergic neurons ($P_{\text{Ca}}/P_{\text{Na}} = 0.10$),

whereas the highest Ca^{2+} permeability was found in subthalamic nucleus neurons ($P_{\text{Ca}}/P_{\text{Na}} = 1.17$). NMDARs of different types of basal ganglia neurons were less variable in their functional properties; those expressed in nigral dopaminergic neurons exhibited the slowest gating (deactivation time constant of predominant fast component $\tau_1 = 150$ msec, 100 μM glutamate), and those of globus pallidus neurons showed the fastest gating ($\tau_1 = 67$ msec). The Mg^{2+} block of NMDARs was similar; the average chord conductance ratio $g_{-60\text{mV}}/g_{+40\text{mV}}$ was 0.18–0.22 in 100 μM external Mg^{2+} . Hence, AMPARs expressed in different types of basal ganglia neurons are markedly diverse, whereas NMDARs are less variable in functional properties that are relevant for excitatory synaptic transmission and neuronal vulnerability.

Key words: AMPA receptors; NMDA receptors; deactivation; desensitization; Ca^{2+} permeability; Mg^{2+} block; basal ganglia neurons; fast application; glutamate

The basal ganglia are composed of several synaptically interconnected subcortical nuclei (the striatum, globus pallidus, substantia nigra, and subthalamic nucleus) that participate in the control of movement. The extrinsic innervation of the basal ganglia, originating in the neocortex and the thalamus, is primarily glutamatergic (for review, see Parent and Hazrati, 1995a,b). By contrast, the intrinsic synaptic circuit of the basal ganglia mainly uses γ -aminobutyrate (GABA) as its transmitter. GABAergic neurons mainly predominate in the striatum, globus pallidus, and substantia nigra pars reticulata, whereas glutamatergic neurons are restricted to the subthalamic nucleus (Rinvik and Ottersen, 1993). In addition, large interneurons of the striatum use acetylcholine, and neurons of the substantia nigra pars compacta use dopamine as transmitters (Yung et al., 1991; Kawaguchi, 1993). Hence, the intrinsic synaptic circuitry of the basal ganglia, unlike that in other CNS regions (hippocampus and neocortex), is based primarily on GABAergic neurons.

In the basal ganglia, as in other brain regions, synaptically released glutamate activates three principal types of glutamate receptors (GluRs): AMPA receptors (AMPA receptors)/kainate recep-

tors, NMDA receptors (NMDARs), and metabotropic glutamate receptors (mGluRs). AMPARs and NMDARs mediate fast synaptic transmission in the basal ganglia (Kawaguchi, 1992; Mori et al., 1994), whereas mGluRs seem to be involved in the induction of long-term changes of synaptic efficacy (Calabresi et al., 1992). In addition, long-lasting activation of GluRs may be important in the pathophysiology of basal ganglia disorders. Activation of AMPARs/kainate receptors and NMDARs leads to excitotoxic neuronal death via GluR-mediated Ca^{2+} inflow (Choi, 1988; Beal et al., 1991; Chen et al., 1995), whereas activation of metabotropic GluRs either enhances or reduces excitotoxicity (for review, see Nicoletti et al., 1996). It was proposed that the action of excitotoxins on GluRs is a main factor in the development of both acute CNS injury (hypoxia, ischemia) and chronic neurological disorders (e.g., Huntington's disease, Parkinson's disease; Young, 1993). This raises the question of whether the selective degeneration of striatal principal neurons in Huntington's disease or nigral dopaminergic neurons in Parkinson's disease could be related to different functional properties of ionotropic GluRs expressed by these neurons.

Several AMPAR, kainate receptor, and NMDAR subunits were identified by molecular cloning (for review, see Hollmann and Heinemann, 1994). In recombinant AMPARs assembled from GluR-A to -D subunits, the Ca^{2+} permeability is determined by the GluR-B subunit (Hollmann and Heinemann, 1994), whereas the gating properties are regulated by GluR-B and GluR-D subunits (Burnashev, 1993; Mosbacher et al., 1994). In recombinant NMDARs assembled from NR1 and NR2A to NR2D subunits, the NR2 subunit confers both the gating prop-

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erties and the strength of Mg^{2+} block (Monyer et al., 1994). *In situ* hybridization and immunocytochemical analysis suggested that different types of basal ganglia neurons express distinct subsets of AMPAR and NMDAR subunits (Martin et al., 1993; Standaert et al., 1994; Landwehrmeyer et al., 1995). The functional properties of the native GluRs in these neurons, however, remain unknown. Using the patch-clamp technique in brain slices, we functionally characterized AMPARs and NMDARs in identified basal ganglia neurons. AMPARs differed substantially in gating and Ca^{2+} permeability, whereas NMDARs were relatively similar with regard to gating and Mg^{2+} sensitivity.

MATERIALS AND METHODS

Brain slice preparation and visualization of different types of neurons in the basal ganglia. Slices 300 μ m thick were cut from the brains of 10- to 15-d-old Wistar rats with a vibratome (Campden, Loughborough, England). Striatal and midbrain slices were cut in the frontal plane, and globus pallidus slices were cut in the parasagittal plane. The mammillary nuclei and the mammillary recess of the third ventricle served as landmarks to distinguish the substantia nigra from the adjacent subthalamic nucleus in midbrain slices. Slices containing the substantia nigra were from the region caudal to the mammillary nuclei and the mammillary recess; the pars reticulata of the substantia nigra was located ventrolaterally, and the pars compacta was located dorsomedially. Slices containing the subthalamic nucleus were from the region directly rostral to the mammillary nuclei, where the mammillary recess of the third ventricle was visible (Paxinos and Watson, 1986). Neurons were identified by infrared differential interference contrast (IR-DIC) videomicroscopy (Stuart et al., 1993) with a Newvicon camera (C2400, Hamamatsu, Hamamatsu City, Japan) and an infrared filter (RG9, Schott, Mainz, Germany) mounted to an upright microscope (Axioskop FS, Zeiss, Oberkochen, Germany).

Patch-clamp recording and fast application of agonists. Patch pipettes were pulled from borosilicate glass tubing (2.0 mm outer diameter, 0.5 mm wall thickness; Hilgenberg, Malsfeld, Germany). When filled with internal solution, they had a resistance of 2–5 M Ω . Identified neurons were approached with patch pipettes under visual control with positive pressure (Stuart et al., 1993). Only neurons with resting potentials more negative than -60 mV were used. To obtain nucleated patches (Sather et al., 1992), we applied negative pressure (100–200 mm Hg) during the withdrawal of the patch pipette. The average diameter of the nucleated patches was 8.6–10.9 μ m in the types of neurons investigated.

Functional properties of AMPARs and NMDARs were investigated via fast application of agonists (Colquhoun et al., 1992) to nucleated patches, with the exception of AMPAR pharmacology and gating that were examined in outside-out patches to achieve the fastest possible solution exchange. The double-barreled application pipette was made from θ glass tubing (2 mm outer diameter, 0.3 mm wall thickness, 0.12 mm septum; Hilgenberg), and the Piezo-electric element used was a PI-275.50 (Physik Instrumente, Waldbronn, Germany) driven by a P-270 high-voltage amplifier. The perfusion rate was 50–70 μ l min $^{-1}$ for experiments on nucleated patches and 200 μ l min $^{-1}$ for experiments on outside-out patches. The exchange time (20–80%), measured with an open-patch pipette during a change between Na^{+} -rich and 10% Na^{+} -rich solution, was 200–300 μ sec for the low flow rate and 50–150 μ sec for the high flow rate. Fast application experiments were started as soon as possible after patch excision (1–2 min after access to the cell interior was obtained). Agonist pulses were applied every 5 or 8 sec. After completion of the experiment, the patch was blown off and the zero current potential was measured; it was less than ± 3 mV.

Membrane currents were recorded with an Axopatch 200A amplifier (Axon Instruments, Foster City, CA). AMPAR-mediated currents were filtered at 2–5 kHz and NMDAR-mediated currents at 1 kHz with the internal four-pole low-pass Bessel filter of the amplifier. Data were digitized and stored on-line with a CED 1401plus interface (CED, Cambridge, England) connected to a personal computer. The sampling frequency was twice the filter frequency. All recordings were made at room temperature (20–24°C). Traces shown represent single sweeps (I - V AMPAR-mediated current), averages from 3 or 6 sweeps (I - V NMDAR-mediated current), or averages from 10–40 sweeps (kinetics of AMPAR- or NMDAR-mediated current).

Analysis. The decay time constants of the AMPAR- and NMDAR-mediated current were determined by least-squares fit of the decay phase

after the peak current. AMPAR deactivation and desensitization time course was evaluated by using a fitting interval of 25 msec (deactivation) and 100 msec (desensitization), respectively; the amplitude of the non-desensitizing current was measured at the end of the 100 msec pulse. NMDAR deactivation time course was analyzed by using a fitting interval of 3000 msec. Data points of the I - V relations were fit by a fifth order polynomial, from which the value of the interpolated reversal potential (V_{rev}) was calculated. Chord conductance ratios ($g_{\Delta V1}/g_{\Delta V2}$; g_{+40mV}/g_{-80mV} for AMPAR-mediated currents and g_{-60mV}/g_{+40mV} for NMDAR-mediated currents) were calculated by using the values of the fit I - V curve at $V_{rev} + \Delta V_{1,2}$. The P_{Ca}/P_{Na} values were calculated from the measured values of the reversal potential after correction for junction potentials and ion activities, as described previously [See Experimental Procedures and equation 1 in Geiger et al. (1995)]. All numerical values denote mean $\pm$ SEM. In the bar graphs, the number of patches is shown in parentheses on top of each bar. Statistical significance was assessed by one-way ANOVA at the significance level indicated.

Biocytin staining and double labeling. To confirm visual identification, we filled subsets of cells with biocytin (Sigma, St. Louis, MO) in K-gluconate internal solution for 30 min in the whole-cell recording configuration. Slices were fixed (12 hr, 4°C) in 0.1 M phosphate buffer (PB) containing 1% paraformaldehyde and 1% glutaraldehyde, incubated (12 hr, 4°C) in avidin-horseradish peroxidase (HRP) complex (ABC-Elite, Camon, Wiesbaden, Germany) and 0.1% Triton X-100 (Merck, Darmstadt, Germany), and finally visualized with 3,3'-diaminobenzidine as a chromogen (Horikawa and Armstrong, 1988). To assess the immunoreactivity of biocytin-filled striatal neurons for choline acetyltransferase (ChAT), we fixed slices (30 min, 4°C) in PB containing 4% paraformaldehyde, 0.1% glutaraldehyde, and 1% saturated picric acid and pretreated them (1 hr, 22°C) with 0.5% Triton X-100 in PB. Then slices were incubated (48 hr, 22°C) in a mixture of rat monoclonal antibody against ChAT (final concentration 3.3 μ g/ml; Boehringer, Mannheim, Germany), 10% goat serum, and 0.1% Triton X-100 and subsequently (24 hr, 22°C) with rhodamine-conjugated avidin (diluted 1:200; Vector, Burlingame, CA) and goat anti-rat fluorescein isothiocyanate (FITC)-conjugated antibody (final concentration 15 μ g/ml; Jackson ImmunoResearch, West Grove, PA). Between the incubation steps, slices were rinsed with PB. After they were washed and mounted in Mowiol (Hoechst, Frankfurt, Germany), double-labeled cells were examined with epifluorescence illumination (Zeiss filter sets 9 and 14). Control experiments performed on three large striatal interneurons indicated that no FITC staining was observed when the antibody against ChAT was replaced by unspecific rat IgG (Sigma).

Solutions and chemicals. Slices were superfused continuously with physiological extracellular solution containing (in mM): 125 NaCl, 25 NaHCO $_3$, 2.5 KCl, 1.25 NaH $_2$ PO $_4$, 2 CaCl $_2$, 1 MgCl $_2$, and 25 glucose, bubbled with 95% O $_2$ /5% CO $_2$. The HEPES-buffered Na^{+} -rich external solution used for fast application contained (in mM): 135 NaCl, 5.4 KCl, 1.8 CaCl $_2$, 1 MgCl $_2$, and 5 HEPES, pH-adjusted to 7.2 with NaOH. The Ca^{2+} -rich external solution contained (in mM): 30 CaCl $_2$, 105 *N*-methyl-D-glucamine (NMDG), and 5 HEPES, pH-adjusted to 7.2 with HCl. To study AMPARs in isolation, we added 50 μ M of the specific NMDAR antagonist D-2-amino-5-phosphonopentanoic acid (D-AP5) to the external solution (both barrels). To study NMDARs in isolation, we either omitted MgCl $_2$ (referred to as Mg^{2+} -free) or reduced it (to 100 μ M) and added 10 μ M glycine and 10 μ M of the specific AMPAR/kainate receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) (both barrels). With these solutions, fast application of glutamate evoked AMPAR- and NMDAR-mediated currents in almost every nucleated patch isolated.

The internal solution was either K^{+} -rich internal solution containing (in mM): 140 KCl, 10 EGTA, 2 MgCl $_2$, 2 Na $_2$ ATP, and 10 HEPES, pH-adjusted to 7.3 with KOH, or Cs^{+} -rich internal solution containing (in mM): 140 CsCl, 10 EGTA, 2 MgCl $_2$, 2 Na $_2$ ATP, and 10 HEPES, pH-adjusted to 7.3 with CsOH. To examine the action potential pattern, we used an internal solution containing 145 KCl, 0.1 EGTA, 2 MgCl $_2$, 2 Na $_2$ ATP, and 10 HEPES, pH-adjusted to 7.3 with KOH in some experiments (see Fig. 2A). The internal solution for intracellular staining contained (in mM): 13 biocytin, 120 K-gluconate, 20 KCl, 10 EGTA, 2 MgCl $_2$, 2 Na $_2$ ATP, and 10 HEPES, pH-adjusted to 7.3 with KOH.

L-AMPA, kainate, CNQX, and D-AP5 were obtained from Tocris (Essex, England); other chemicals were from Sigma or Merck. Stock solutions of 100 mM glutamate and kainate and 25 mM AMPA were prepared either in distilled water or in the final solution; the pH was adjusted with NaOH or NMDG (free base), depending on the major cation in the final solution.

Figure 1. Identification of the main types of neurons in the basal ganglia circuitry. *Center*, Schematic drawing of the main components comprising the basal ganglia and their glutamatergic synaptic innervation (Parent and Hazrati, 1995a,b). *Left and right*, IR-DIC images of neurons in different components of the basal ganglia. *Str-PN*, Medium-sized striatal principal neurons; *Str-IN*, large striatal putative cholinergic interneurons (~2% of all striatal neurons); *SNR*, substantia nigra pars reticulata, putative GABAergic neurons; *SNC*, substantia nigra pars compacta, putative dopaminergic neurons; *GP*, globus pallidus neurons; *STN*, subthalamic nucleus neurons. The size of the somata of these basal ganglia neurons is in agreement with published morphological properties. Measured and published soma diameters were as follows: *Str-PN*, 13–16 μm (13 μm ; Kawaguchi, 1993); *Str-IN*, 23–34 μm (27 μm ; Kawaguchi, 1993); *SNR*, 20–25 μm longitudinal diameter $\times$ 10–15 μm transverse diameter (20 μm , Poirier et al., 1983); *SNC*, 20–25 μm (34 $\times$ 20 μm ; Yung et al., 1991); *GP*, 31–43 μm $\times$ 14–23 μm (25–40 μm $\times$ 15–25 μm ; Millhouse, 1986); and *STN*, 10–15 μm (17 μm ; Afsharpoor, 1985).

RESULTS

Identification of the main types of neurons in the basal ganglia

Figure 1 shows a schematic drawing of the main components of the basal ganglia circuitry and their glutamatergic synaptic connections. Using IR-DIC videomicroscopy (Stuart et al., 1993), we identified the different cell types in this circuitry primarily on the basis of their location and the size and shape of their somata (Fig. 1 and legend). In the striatum, the somata of putative GABAergic principal neurons were medium-sized and spherical (*Str-PN*), whereas those of putative cholinergic interneurons were much larger and polygonal (*Str-IN*). In the substantia nigra, the somata of putative GABAergic neurons were relatively small and fusiform (*SNR*), whereas those of putative dopaminergic neurons were larger and polygonal (*SNC*). In the globus pallidus adjacent to the striatum, mostly neurons with exceptionally large polygonal somata (*GP*) were found. In the subthalamic nucleus adjacent to the substantia nigra, neurons with

medium-sized spherical somata predominated (*STN*). In addition to soma size, the different types of neurons in the basal ganglia could be distinguished by the shape of their dendrites. Putative GABAergic neurons of the substantia nigra mostly had two, and globus pallidus neurons typically had four thick primary dendrites that could be followed for ~100 micrometers in the IR-DIC image. By contrast, the other types of neurons exhibited thinner and less clearly visible dendritic processes.

To confirm the visual identification of cell types on the basis of the IR-DIC image, we measured the action potential pattern in the current-clamp configuration before patch excision. In the striatum, principal neurons generated a train of action potentials on sustained injection of a depolarizing current (Fig. 2*A*, top trace), whereas putative cholinergic interneurons produced only a few action potentials, each followed by a marked and long-lasting afterhyperpolarization (Fig. 2*A*, bottom trace; Kawaguchi, 1993). In the substantia nigra, putative GABAergic neurons fired action

Figure 2. Confirmation of visual identification of striatal neurons by electrophysiological properties, biocytin staining, and immunocytochemistry. *A*, Membrane potential changes in response to injection of 0.5 sec hyperpolarizing and depolarizing current pulses. Whole-cell current-clamp recording. *Top traces* are from a medium-sized striatal principal neuron, and *bottom traces* are from a large striatal interneuron. Currents injected were $-50/130$ and $-60/120$ pA, respectively. The resting potentials of the two cells were -71 and -64 mV; the membrane potentials were set to -70 mV (*dashed lines*) by injection of a small constant current. Note the marked afterhyperpolarization that follows each single action potential in the striatal interneuron. *B*, Camera lucida drawing of a large striatal interneuron filled with biocytin. The soma and the dendrites of the cell are drawn in black; the axonal arborization is drawn in red. The arrow points to the axon close to its origin at one of the primary dendrites. The filled circle in the inset indicates the location of the soma of the filled neuron (Str, striatum; LV, lateral ventricle; Cor, neocortex; D, dorsal; L, lateral). *C*, Fluorescence microphotographs of a large striatal interneuron filled intracellularly with biocytin and double-labeled with rhodamine-conjugated avidin (*left*, epi-illumination, 510–560 nm) and rat monoclonal antibody against ChAT/FITC-conjugated goat anti-rat antibody (*right*, epi-illumination, 450–490 nm).

potentials at a maximal frequency of 30–50 Hz during depolarization, whereas dopaminergic neurons exhibited a characteristic sag during hyperpolarization (Yung et al., 1991) (data not shown).

Globus pallidus neurons exhibited an action potential pattern similar to that of nigral GABAergic neurons, but the degree of adaptation was more variable, in agreement with published results

Figure 3. Activation of AMPARs in basal ganglia neurons by different agonists. *A*, Traces of currents activated by 100 msec pulses of 1 mM glutamate, AMPA, and kainate in outside-out patches isolated from nigral dopaminergic neurons. Glutamate- and kainate-activated current are from the same patch, and AMPA-activated current is from a different patch. *B*, Bar graph of the average amplitude of the nondesensitizing current component relative to that of the respective peak current activated by 1 mM glutamate, AMPA, and kainate for the populations of basal ganglia neurons investigated. The amplitude of the nondesensitizing current was measured at the end of the 100 msec agonist pulse. *C*, Cross-desensitization of kainate-activated currents by AMPA in a nucleated patch isolated from a subthalamic nucleus neuron. *Top* and *bottom* traces, Current activated by 500 μ M AMPA. *Middle* trace, Application of 1 mM kainate in the maintained presence of 500 μ M AMPA did not evoke detectable currents; recording was obtained between *top* and *bottom* traces from the same nucleated patch. Membrane potential, -60 mV; Na^+ -rich external solution (50 μ M D-AP5) in all experiments.

(Nambu and Llinás, 1994). Subthalamic nucleus neurons showed a characteristic rebound burst of up to five action potentials after hyperpolarizing pulses (Nakanishi et al., 1987; Yung et al., 1991) (data not shown).

In the striatum, visual identification of neuron types was confirmed further by intracellular staining and by immunocytochemical analysis. Light microscopic examination of putative cholinergic striatal interneurons filled with biocytin revealed that their dendrites were sparsely spiny or aspiny (12 of 12 cells; Fig. 2*B*). The axonal arborization was local and confined to a region of <500 μ m around the soma, with no obvious projections outside the striatum (Fig. 2*B*). Choline acetyltransferase (ChAT) immunoreactivity was detected in the majority of biocytin-filled large striatal neurons examined (13 of 14 cells tested were positive for ChAT; Fig. 2*C*). These morphological and

immunocytochemical properties indicated that the large striatal neurons were cholinergic interneurons.

Activation of AMPARs in basal ganglia neurons by different agonists

To investigate the functional properties of GluRs present in the somatic membrane of basal ganglia neurons, we used fast application of agonists to nucleated (Sather et al., 1992) and conventional outside-out membrane patches. In conditions that allowed us to study AMPA/kainate receptors in isolation (1 mM external Mg^{2+} and 50 μ M D-AP5; membrane potential, -60 mV), 100 msec pulses of 1 mM glutamate, AMPA, or kainate evoked currents in outside-out patches in all types of basal ganglia neurons investigated. In Figure 3*A*, this is exemplified for nigral dopami-

Figure 4. AMPARs expressed in different types of basal ganglia neurons differ in deactivation and desensitization kinetics. *A*, Traces of current activated by 1 msec glutamate pulses in outside-out patches. *Top trace*, Striatal principal neuron patch; *bottom trace*, globus pallidus neuron patch. *B*, Bar graph of average deactivation time constants of AMPAR-mediated currents in the types of basal ganglia neurons investigated. *C*, Traces of current activated by 100 msec glutamate pulses in outside-out patches. *Top trace*, Striatal principal neuron patch; *bottom trace*, striatal cholinergic interneuron patch. *D*, Bar graph of average desensitization time constants of AMPAR-mediated currents in the types of basal ganglia neurons investigated. All data are from outside-out patches. Membrane potential, -60 mV; glutamate concentration, 1 mM; Na^+ -rich external solution (50 μM D-AP5) in all experiments.

nergic neurons. Currents produced by 100 msec pulses of glutamate or AMPA were very similar, showing a rapid rise (20–80% rise time 200–400 μsec), followed by a slower, almost complete desensitization (Fig. 3*A*, *top* and *middle* traces). For both agonists, the amplitude of the nondesensitizing current remaining at the end of the pulse was 0.4–7.4% of the peak current amplitude measured at the beginning of the pulse (Fig. 3*B*).

By contrast, currents activated by 100 msec pulses of 1 mM kainate were much smaller in amplitude than those activated by glutamate or AMPA and were only weakly desensitizing (Fig. 3*A*, *bottom* trace). The average amplitude of the nondesensitizing current measured at the end of a 100 msec kainate pulse was 60–90% of the respective peak current amplitude at the beginning of the pulse in the populations of neurons investigated (Fig. 3*B*).

Maintained application of AMPA resulted in a complete cross-desensitization of kainate-activated currents in nucleated patches isolated from all types of neurons examined. In Figure 3*C*, this is exemplified for a patch from a subthalamic nucleus neuron. In the presence of 500 μM AMPA, application of 1 mM kainate did not activate detectable currents (*middle* trace), whereas pulses of 500 μM AMPA produced large inward currents in the same patch (*top* and *bottom* traces). Identical results were obtained for the other types of neurons (3–5 patches for each cell type). This indicates that the currents activated by glutamate, AMPA, and kainate in basal ganglia neurons are mediated by AMPARs, similar to those in hippocampal neurons (Patneau and Mayer, 1991; Patneau et al., 1993).

Table 1. Functional properties of AMPARs in neurons of the basal ganglia

Cell type	Deactivation τ (msec)	Desensitization τ (msec)	P_{Ca}/P_{Na}	Rectification index (g_{+40mV}/g_{-80mV})	Peak current NP, –60 mV (pA)
Striatum					
Striatal principal neurons	2.2 ± 0.1 (10)	11.5 ± 0.9 (10)	0.11 ± 0.00 (9)	0.93 ± 0.02 (9)	692 ± 95 (9)
Striatal cholinergic interneurons	1.2 ± 0.1 (10)	3.6 ± 0.4 (10)	1.16 ± 0.16 (10)	0.49 ± 0.06 (10)	246 ± 18 (10)
Substantia nigra					
Nigral GABAergic neurons	1.7 ± 0.2 (8)	3.6 ± 0.3 (9)	0.11 ± 0.01 (8)	1.08 ± 0.17 (7)	326 ± 46 (7)
Nigral dopaminergic neurons	1.6 ± 0.1 (8)	6.1 ± 0.8 (9)	0.10 ± 0.01 (6)	1.01 ± 0.07 (7)	571 ± 90 (7)
Globus pallidus and subthalamic nucleus					
Globus pallidus neurons	1.1 ± 0.1 (5)	5.1 ± 0.8 (5)	0.67 ± 0.14 (7)	0.70 ± 0.06 (7)	166 ± 60 (7)
Subthalamic nucleus neurons	1.6 ± 0.1 (8)	3.6 ± 0.4 (9)	1.17 ± 0.30 (6)	0.60 ± 0.06 (6)	285 ± 60 (6)

Deactivation and desensitization time constants of AMPARs were determined using 1 and 100 msec pulses of glutamate, respectively. The P_{Ca}/P_{Na} of AMPARs was calculated from the shift of reversal potential of glutamate-activated currents on exchange of Na^+ -rich by Ca^{2+} -rich (30 mM) external solution. The rectification index of the AMPAR-mediated current, g_{+40mV}/g_{-80mV} , was determined in Na^+ -rich external solution. The peak current amplitude at –60 mV was determined in Na^+ -rich external solution. All data were obtained from nucleated patches (NP) using 3 mM glutamate, with the exception of AMPAR kinetics, which was studied in outside-out patches using 1 mM glutamate.

Gating properties of AMPARs expressed in basal ganglia neurons

Although their pharmacological properties were similar, AMPARs expressed in different types of basal ganglia neurons differed in their gating properties (deactivation and desensitization). In Figure 4, this is exemplified for outside-out patches isolated from the cell types that express AMPARs with the most divergent gating kinetics. The deactivation of AMPARs after 1 msec pulses of glutamate was twofold faster in patches isolated from globus pallidus neurons than in those from striatal principal neurons (average deactivation time constant $\tau = 1.1$ vs 2.2 msec, 1 mM glutamate; Fig. 4A, Table 1). The average deactivation τ in the other types of basal ganglia neurons (striatal cholinergic interneurons, nigral GABAergic neurons, nigral dopaminergic neurons, and subthalamic nucleus neurons) ranged from 1.2 to 1.7 msec (Fig. 4B, Table 1).

The desensitization of AMPARs during 100 msec pulses of glutamate was approximately threefold faster in outside-out patches isolated from striatal cholinergic interneurons, nigral GABAergic neurons, and subthalamic nucleus neurons than in those from striatal principal neurons (average desensitization $\tau = 3.6$ vs 11.5 msec, 1 mM glutamate; Fig. 4C, Table 1). The average desensitization τ in the other classes of cells ranged from 5.1 to 6.1 msec (Fig. 4D, Table 1). The differences in both deactivation and desensitization τ among the cell populations investigated were highly significant ($p < 2 \cdot 10^{-4}$ and $p < 10^{-4}$, respectively, one-way ANOVA).

Ca^{2+} permeability and current rectification of AMPARs in basal ganglia neurons

AMPARs expressed in different types of basal ganglia neurons differed markedly in their permeability to Ca^{2+} . This is exemplified by nigral dopaminergic neurons that express AMPARs with the lowest Ca^{2+} permeability (Fig. 5A) and by subthalamic nucleus neurons that express AMPARs with the highest Ca^{2+} permeability (Fig. 5B, Table 1). In Na^+ -rich external solution, the reversal potential of the AMPAR-mediated peak current was close to 0 mV for nucleated patches isolated from both cell types (-3.5 ± 0.7 mV and -1.1 ± 1.0 mV). When the Na^+ -rich external solution was exchanged with a Ca^{2+} -rich solution, the reversal potential of the glutamate-activated peak current shifted to negative values in dopaminergic neuron patches but changed very little in subthalamic nucleus neuron patches (reversal potentials in Ca^{2+} -rich solution were -68.0 ± 1.2 mV and -15.0 ± 4.4 mV, respectively; Fig. 5A, B). The P_{Ca}/P_{Na} value calculated from the shift in reversal potential was ~ 10 -fold

higher for subthalamic nucleus neuron AMPARs ($P_{Ca}/P_{Na} = 1.17$) than for nigral dopaminergic neuron AMPARs ($P_{Ca}/P_{Na} = 0.10$; Fig. 5C, Table 1). In striatal cholinergic interneurons and in globus pallidus neurons, AMPARs were also highly permeable to Ca^{2+} ($P_{Ca}/P_{Na} = 0.67$ – 1.16), whereas in striatal principal neurons and nigral GABAergic neurons the Ca^{2+} permeability of AMPARs was low ($P_{Ca}/P_{Na} = 0.11$; Fig. 5C, Table 1).

Correlated with their relative Ca^{2+} permeability, AMPARs expressed in different types of basal ganglia neurons differed in the shape of the I - V relation of glutamate-activated peak current in Na^+ -rich external solution. AMPARs with low Ca^{2+} permeability in nucleated patches isolated from striatal principal neurons and nigral GABAergic and nigral dopaminergic neurons had a virtually linear I - V relation; the average values of the rectification index (g_{+40mV}/g_{-80mV}) were close to unity (0.93 – 1.08 ; Table 1). By contrast, AMPARs with high Ca^{2+} permeability in nucleated patches from subthalamic nucleus neurons, striatal cholinergic interneurons, and globus pallidus neurons had a doubly rectifying I - V relation with a region of reduced slope between 0 and +40 mV (Fig. 5B). Accordingly, the average values of the rectification index were between 0.49 and 0.70 (Table 1). The differences in both Ca^{2+} permeability and rectification index among different types of basal ganglia neurons were highly significant ($p < 10^{-4}$ in both cases; one-way ANOVA).

Gating properties of NMDARs expressed in basal ganglia neurons

In conditions that allowed us to study NMDARs in isolation (Mg^{2+} -free external solution, 10 μ M glycine, and 10 μ M CNQX), 10 msec pulses of 100 μ M glutamate activated currents in nucleated patches with a rising phase of ~ 10 msec duration (20–80% rise time, 5.7–8.3 msec), followed by a substantially slower deactivation that was biexponential in all types of basal ganglia neurons investigated. The values of the deactivation time constants, however, differed among the cell types examined. This is exemplified by the NMDARs expressed in nigral dopaminergic neurons that showed the slowest deactivation (Fig. 6A) and those in globus pallidus neurons that showed the fastest deactivation (Fig. 6B). The average time constants of both the fast and the slow component of deactivation were approximately twofold lower in nucleated patches from globus pallidus neurons ($\tau_1 = 67$ msec and $\tau_2 = 382$ msec, contributing 59 and 41% to the total decay amplitude, respectively; Table 2) than in patches from nigral dopaminergic

Figure 5. AMPARs expressed in different types of basal ganglia neurons differ in Ca^{2+} permeability. *A, B*, I - V relations of glutamate-activated peak currents recorded from nucleated patches in Na^+ -rich (open circles) and Ca^{2+} -rich (30 mM, filled circles) external solution. *A*, Patch from a dopaminergic neuron of the substantia nigra pars compacta. *B*, Patch from a subthalamic nucleus neuron. Recordings of glutamate-activated currents at -100 mV and $+50$ mV are shown as inset: top traces in Na^+ -rich solution and bottom traces in Ca^{2+} -rich external solution. The continuous curves represent polynomials of the fifth order fit to the data points. Reversal potentials in Ca^{2+} -rich solution are indicated by arrows. *C*, Bar graph of the average relative Ca^{2+} permeability (P_{Ca}/P_{Na}) of AMPARs expressed in the types of basal ganglia neurons investigated, determined from the reversal potentials of glutamate-activated currents in Na^+ -rich and Ca^{2+} -rich external solution. All data are from nucleated patches. External solutions contained $50 \mu M$ D-AP5 in all cases.

neurons ($\tau_1 = 150$ msec and $\tau_2 = 1049$ msec, contributing 66 and 34% to the total decay amplitude; Table 2). In the other types of neurons (striatal principal neurons, striatal cholinergic interneurons, nigral GABAergic neurons, and subthalamic nucleus neurons), the deactivation time course was similar to that of NMDARs in nigral dopaminergic neurons (Fig. 6C, Table 2). ANOVA tests revealed significant differences among the populations of neurons in τ_1 ($p < 0.005$), in τ_2 ($p < 0.05$), and in the total charge carried by the two components ($A_1 \cdot \tau_1 + A_2 \cdot \tau_2$, in which A_1 and A_2 denote the relative amplitudes of the two components; $p < 0.05$). No significant differences, however, were found with respect to the values of A_1 and A_2 ($p > 0.1$).

Mg^{2+} block of NMDARs in basal ganglia neurons

Although the deactivation time course of NMDARs differed among basal ganglia neurons, their Mg^{2+} sensitivity was similar. This was assessed from the shape of the I - V relation of NMDAR-mediated currents in Na^+ -rich external solution containing $100 \mu M$ Mg^{2+} . As an example, Figure 7A shows a peak I - V relation of NMDAR-mediated currents in a nucleated patch isolated from a subthalamic nucleus neuron. Glutamate-activated currents reversed close to 0 mV and showed a region of negative slope conductance at membrane potentials below -40 mV (Fig. 7A), caused by the voltage-dependent block by external Mg^{2+} . Similar results were obtained for the other types of basal ganglia neurons investigated; the average values of the rectification index g_{-60mV}/g_{+40mV} were between 0.18 and 0.22 (Fig. 7B, Table 2) but were

not significantly different among the populations of basal ganglia neurons investigated ($p > 0.5$; one-way ANOVA). This indicates that NMDARs expressed in all types of basal ganglia neurons are blocked by external Mg^{2+} with high sensitivity.

DISCUSSION

Both AMPARs and NMDARs are present in the somatic membrane of basal ganglia neurons. The present paper provides, to our knowledge, the first description of their gating and permeation properties. AMPARs are markedly diverse, whereas NMDARs are less variable in their functional characteristics.

Functional properties of AMPARs and NMDARs expressed in basal ganglia neurons

AMPARs expressed in different types of basal ganglia neurons differed in their gating properties. Deactivation and desensitization of AMPARs in striatal principal neurons were slow (deactivation $\tau = 2.2$ msec and desensitization $\tau = 11.5$ msec; Table 1), resembling AMPAR gating in hippocampal and neocortical pyramidal cells (deactivation $\tau = 2.5$ – 3.0 msec and desensitization $\tau = 11.2$ – 15.2 msec) (Hestrin, 1993; Geiger et al., 1995). By contrast, deactivation and desensitization of AMPARs expressed in the other types of basal ganglia neurons were much faster (deactivation $\tau = 1.1$ – 1.7 msec and desensitization $\tau = 3.6$ – 6.1 msec; Table 1), comparable to AMPAR gating in hippocampal and neocortical GABAergic interneurons (deactivation $\tau = 1.4$ – 2.1 msec and

Figure 6. NMDARs expressed in different types of basal ganglia neurons differ in gating kinetics. *A, B*, Traces of current activated by 10 msec pulses of 100 μ M glutamate in nucleated patches and the biexponential function fit to the decay phase (3), shown superimposed with its exponential components (1, 2). *A*, Patch from a dopaminergic neuron of the substantia nigra pars compacta; $\tau_1 = 166$ msec (64%) and $\tau_2 = 1158$ msec (36%). *B*, Patch from a globus pallidus neuron; $\tau_1 = 66$ msec (78%) and $\tau_2 = 356$ msec (22%). *C*, Bar graphs of the average time constants of the predominant fast component (τ_1 , top panel) and the slow component (τ_2 , bottom panel) of deactivation of NMDARs in the populations of basal ganglia neurons investigated. All data are from nucleated patches. Membrane potential, -60 mV; Na^+ -rich external solution (Mg^{2+} -free, 10 μ M glycine, and 10 μ M CNQX) in all cases.

desensitization $\tau = 3.3$ – 6.1 msec) (Hestrin, 1993; Livsey et al., 1993; Jonas et al., 1994; Geiger et al., 1995).

AMPA receptors expressed in different types of basal ganglia neurons also differed markedly in their Ca^{2+} permeability. AMPARs in striatal principal neurons and nigral GABAergic and dopaminergic neurons were almost impermeable to Ca^{2+} ($P_{\text{Ca}}/P_{\text{Na}} = 0.10$ – 0.11 ; Table 1), like those in hippocampal and neocortical pyramidal neurons (0.07–0.10; Geiger et al., 1995; Mayer and Westbrook, 1987). Surprisingly, AMPARs expressed in striatal cholinergic interneurons, subthalamic nucleus neurons, and globus pallidus neurons were highly Ca^{2+} permeable ($P_{\text{Ca}}/P_{\text{Na}} = 0.67$ – 1.17 ; Table 1); the $P_{\text{Ca}}/P_{\text{Na}}$ value was comparable to that reported for hippocampal and neocortical GABAergic interneurons [0.69–1.59; Geiger et al. (1995), recorded under experimental conditions identical to those in the present paper].

In the hippocampus and neocortex, the neuron types that express Ca^{2+} -permeable AMPARs are characterized by three main properties: the use of GABA as their transmitter, the specific expression of Ca^{2+} -binding proteins (parvalbumin, calbindin, or calretinin), and the generation of high-frequency trains of action potentials on sus-

tained injection of depolarizing current (for review, see Jonas and Burnashev, 1995). In the basal ganglia, a more complex picture emerges. First, the neurons that express Ca^{2+} -permeable AMPARs are thought to use various transmitters (acetylcholine, GABA, and glutamate; Parent and Hazrati, 1995a,b). Second, these neurons also differ in their content of Ca^{2+} -binding proteins and their action potential pattern. Whereas globus pallidus neurons and subthalamic nucleus neurons generate trains of action potentials on sustained injection of depolarizing current and are positive for parvalbumin (Celio, 1990), striatal cholinergic interneurons produce only a few action potentials separated by long-lasting afterhyperpolarizations (Fig. 2*A*) and do not express parvalbumin, calbindin, or calretinin (Kawaguchi et al., 1995).

Functional differences among NMDARs expressed in different types of basal ganglia neurons also were noted but were much smaller than among AMPARs. NMDARs expressed in basal ganglia neurons deactivated with time constants $\tau_1 = 130$ – 150 msec and $\tau_2 = 687$ – 1088 msec (Table 2), with the exception of NMDARs in globus pallidus neurons that showed significantly faster deactivation ($\tau_1 = 67$ msec and $\tau_2 = 382$ msec; Table 2). In all types of basal ganglia neurons, NMDAR deactivation was

Table 2. Functional properties of NMDARs in neurons of the basal ganglia

Cell type	Deactivation τ_1 (msec)	τ_2 (msec)	Amplitude fast (%)	Mg ²⁺ block (g_{-60mV}/g_{+40mV})	Peak current NP, –60 mV (pA)
Striatum					
Striatal principal neurons	147 ± 19	1088 ± 255 (5)	73 ± 4	0.21 ± 0.01 (7)	65 ± 12 (7)
Striatal cholinergic interneurons	130 ± 18	687 ± 110 (6)	61 ± 3	0.20 ± 0.02 (8)	59 ± 13 (6)
Substantia nigra					
Nigral GABAergic neurons	142 ± 5	797 ± 158 (5)	70 ± 2	0.22 ± 0.01 (6)	137 ± 44 (5)
Nigral dopaminergic neurons	150 ± 12	1049 ± 107 (7)	66 ± 4	0.21 ± 0.03 (8)	154 ± 31 (7)
Globus pallidus and subthalamic nucleus					
Globus pallidus neurons	67 ± 10	382 ± 80 (6)	59 ± 6	0.21 ± 0.02 (6)	60 ± 14 (6)
Subthalamic nucleus neurons	137 ± 16	833 ± 225 (6)	73 ± 6	0.18 ± 0.03 (6)	169 ± 61 (7)

The deactivation time constants of NMDARs were determined by using 10 msec pulses of 100 μ M glutamate in Mg²⁺-free Na⁺-rich external solution and fitting the decay phase with the sum of two exponentials. The contribution of the fast component to the total decay amplitude also was assessed from the biexponential fit. The rectification index of the NMDAR-mediated current, g_{-60mV}/g_{+40mV} , was determined from the I - V relation in Na⁺-rich external solution containing 100 μ M Mg²⁺. The peak current amplitude at –60 mV was determined in Mg²⁺-free Na⁺-rich external solution. All data were obtained from nucleated patches (NP).

faster than in hippocampal pyramidal neurons (τ_1 = 175–288 msec and τ_2 = 1190–2920 msec; Spruston et al., 1995).

NMDARs expressed in basal ganglia neurons were highly sensitive to external Mg²⁺, like those in hippocampal and neocortical pyramidal neurons and interneurons (Nowak et al., 1984; Koh et al., 1995; Spruston et al., 1995). The rectification index g_{-60mV}/g_{+40mV} of NMDAR-mediated currents in the presence of 100 μ M external Mg²⁺ was 0.18–0.22 (Table 2), not significantly different among the populations of neurons examined.

Putative subunit composition of native AMPARs and NMDARs in the basal ganglia

Immunocytochemical analysis indicated that AMPARs in different types of basal ganglia neurons differ in their subunit composition (Petralia and Wenthold, 1992; Martin et al., 1993). Striatal principal neurons express predominantly GluR-A and -B/C subunit protein, whereas striatal cholinergic interneurons express GluR-A and -D. Nigral GABAergic neurons are positive for GluR-A, -B/C, and -D, whereas dopaminergic neurons are enriched in GluR-A and GluR-B/C. Globus pallidus neurons mostly express GluR-A subunit protein, but subsets of cells also express GluR-B/C and -D. Finally, subthalamic nucleus neurons predominantly express GluR-A (Martin et al., 1993).

These immunocytochemical results are consistent with the previous suggestion that the GluR-B subunit in the flip splice version is a determinant of slow gating, whereas the GluR-D subunit, particularly in the flop version, is a determinant of rapid gating of both recombinant AMPARs (Burnashev, 1993; Mosbacher et al., 1994; Partin et al., 1994) and native AMPARs (Geiger et al., 1995). In the basal ganglia, striatal principal neurons express high levels of GluR-B/C, but not GluR-D, resulting in the formation of AMPARs with the slowest gating, whereas striatal cholinergic interneurons express undetectable levels of GluR-B/C and high amounts of GluR-D, leading to the assembly of AMPARs with the fastest gating in the basal ganglia. GluR-D subunits apparently dominate over GluR-B subunits in heteromeric combinations, as suggested by the rapid gating of AMPARs expressed in nigral GABAergic neurons (Table 1).

The results are also consistent with the hypothesis that the GluR-B subunit determines both Ca²⁺ permeability and current rectification of recombinant and native AMPARs (for review, see Hollmann and Heinemann, 1994; Jonas and Burnashev, 1995). Striatal principal neurons and nigral GABAergic and dopaminergic neurons express GluR-B/C subunits at high levels, resulting in the formation of

AMPARs with low Ca²⁺ permeability and linear conduction properties. Striatal cholinergic interneurons, subthalamic nucleus neurons, and possibly globus pallidus neurons express low amounts of GluR-B/C subunits, leading to the formation of highly Ca²⁺-permeable receptors with inwardly or doubly rectifying I - V relations (for review, see Jonas and Burnashev, 1995).

In situ hybridization studies indicated differential expression of NMDAR subunits and splice variants (Standaert et al., 1994; Landwehrmeyer et al., 1995). The NR1 subunit is expressed abundantly in all types of basal ganglia neurons. The C-terminal deletion variant (NR1_{ΔC}), however, is expressed selectively in striatal principal neurons, whereas the N-terminal insertion variant (NR1_{ΔN}) is found exclusively in subthalamic nucleus neurons (Standaert et al., 1994). Striatal principal neurons express predominantly NR2B subunit mRNA, together with small amounts of NR2A mRNA, whereas the other cell types investigated predominantly express NR2D, together with small amounts of NR2B and NR2C (Standaert et al., 1994; Landwehrmeyer et al., 1995).

Given the differential expression of NR1 splice variants and NR2 subunits, it was surprising that only relatively minor functional differences of NMDAR properties among different cell types were observed. Unlike the native receptors, recombinant NMDARs assembled from different subunits differ in their gating kinetics and Mg²⁺ sensitivity. Deactivation of recombinant NR1/NR2D receptors is slower than that of recombinant NR1/NR2A, NR2B, or NR2C receptors (τ = 4.8 vs 120–400 msec; Monyer et al., 1994), and the Mg²⁺ sensitivity of recombinant NR1/NR2C and NR2D NMDARs is lower than that of NR1/NR2A and NR2B NMDARs (Ishii et al., 1993; Monyer et al., 1994). Native NMDARs in striatal principal neurons (presumably NR1/NR2B heteromeric receptors), however, were not different from those in striatal cholinergic interneurons, nigral GABAergic and dopaminergic neurons, and subthalamic nucleus neurons (possibly NR1/NR2D receptors) in the functional characteristics examined. Conversely, the difference in NMDAR deactivation kinetics between globus pallidus neurons (possibly NR1/NR2D receptors) and the other cell types could not be traced back to any known difference in subunit composition. A possible explanation may be that the NR2B subunit is dominant in determining the functional properties of heteromeric NMDARs, because all types of neurons in the basal ganglia express NR2B, albeit in small amounts. It cannot be excluded, however, that certain NMDAR subunits are targeted to

Figure 7. NMDARs expressed in basal ganglia neurons show similar sensitivity to external Mg^{2+} . *A*, *I*-*V* relation of glutamate-activated peak currents in Na^+ -rich external solution containing $100 \mu\text{M}$ Mg^{2+} in a nucleated patch isolated from a subthalamic nucleus neuron. Traces of glutamate-activated currents at membrane potentials varied from -100 mV to $+40$ mV in 20 mV steps are shown as *inset*. The *continuous curve* represents a polynomial of the fifth order fit to the data points. *B*, Bar graph of the average rectification index, $g_{-60\text{mV}}/g_{+40\text{mV}}$, of the NMDAR-mediated current in the types of basal ganglia neurons investigated. All data are from nucleated patches. Na^+ -rich external solution ($100 \mu\text{M}$ external Mg^{2+} , $10 \mu\text{M}$ glycine, and $10 \mu\text{M}$ CNQX) in all experiments.

peripheral dendrites or presynaptic elements and thus may be absent from nucleated patches.

Functional significance: cell-specific regulation of glutamatergic synaptic transmission and selective vulnerability

The present results suggest that excitatory synaptic currents in different types of neurons of the basal ganglia circuitry are mediated by functionally distinct AMPARs and NMDARs. On the basis of the difference in deactivation and desensitization time course, it is expected that AMPARs in striatal principal neurons will mediate relatively slow EPSCs, whereas AMPARs in all other types of basal ganglia neurons may generate faster EPSCs, similar to those in neurons of other motor systems (e.g., cerebellar granule cells; Silver et al., 1996). In striatal principal neurons and nigral GABAergic and dopaminergic neurons, synaptic activation is expected to produce Ca^{2+} inflow through NMDARs, but not AMPARs, whereas in the other types of neurons, synaptically released glutamate very likely activates a dual pathway of GluR-mediated Ca^{2+} entry. It seems possible, therefore, that excitatory synapses in the basal ganglia exhibit different forms of synaptic plasticity, dependent on the functional properties of their postsynaptic GluRs (Gu et al., 1996).

Activation of AMPARs, NMDARs, and certain subtypes of mGluRs by sustained elevation of glutamate leads to a rise in intracellular Ca^{2+} concentration that is thought to trigger excitotoxin-mediated neuronal death (Choi, 1988). Although the presence of AMPARs and NMDARs in all types of basal ganglia neurons is consistent with this view, our results cannot explain cell-specific differences in vulnerability directly. After acute application of excitotoxins *in vitro*, striatal principal neurons degenerate, whereas cholinergic interneurons are preserved (Beal et al., 1991). Chronic neurodegenerative disorders, e.g., Huntington's and Parkinson's disease, also specifically affect certain cell types (striatal principal neurons and nigral dopaminergic neurons, re-

spectively; Young, 1993). Hence, the types of basal ganglia neurons expressing Ca^{2+} -permeable AMPARs seem to be less vulnerable than those expressing Ca^{2+} -impermeable AMPARs. A relation may exist, however, between the gating kinetics of GluRs and the vulnerability of neurons, because the cell types expressing AMPARs and NMDARs with the slowest gating seem to be the most susceptible. Various additional factors, however, including metabotropic GluRs or Ca^{2+} -binding proteins, may contribute to selective neuronal degeneration.

A hallmark of several basal ganglia diseases is the disturbed balance between the activity of the "direct pathway" that facilitates movement and the "indirect pathway" that inhibits movement via the subthalamic nucleus (Albin et al., 1989). Because the function of the indirect pathway is dependent on both the stimulation by acetylcholine released from striatal interneurons and the activity of subthalamic nucleus neurons, a block of Ca^{2+} -permeable AMPARs may result in selective suppression of the indirect pathway. Hence, substances blocking Ca^{2+} -permeable AMPARs, perhaps derived from polyamine toxins (Blaschke et al., 1993), may be useful agents in the treatment of basal ganglia diseases.

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