Heterogeneity in Use-Dependent Depression of Inhibitory Postsynaptic Potentials in the Rat Neostriatum In Vitro

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Heterogeneity in use-dependent depression of inhibitory postsynaptic potentials in the rat neostriatum in vitro. J. Neurophysiol. 77: 427–434, 1997. “Minimal stimulation” was applied to evoke responses in an “all-or-none” fashion in presumed medium spiny neurons of rat neostriatal slices in the presence of antagonists for glutamatergic excitation. For comparison, responses were evoked in the same cells by compound stimulation. Bicuculline (30 μM) blocked responses evoked by minimal stimulation, indicating that they were γ-amino-butyric acid-A (GABAₐ) receptor-mediated inhibitory postsynaptic potentials (IPSPs), whereas responses evoked by compound stimulation were only reduced in amplitude. Likewise, R(-)baclofen (1–20 μM) blocked IPSPs evoked by minimal stimulation in all but one cell. On the contrary, responses evoked by compound stimulation were always reduced in amplitude but never blocked. Paired-pulse depression (PPD) of averaged responses to minimal and compound stimulation was observed at a stimulus interval of 300 ms. The GABAₐ receptor antagonist CGP55845A (0.5 μM) had no effect on PPD evoked by compound stimulation but abolished PPD evoked by minimal stimulation. In a second set of experiments, the two stimulation paradigms were used to evoke responses in neostriatal slices continuously bathed in R(-)baclofen (10–20 μM). In R(-)baclofen a strong PPD was evoked by minimal and by compound stimulation. The amplitude of the response to compound stimulation increased on application of CGP55845A (0.5 μM). At the same time, PPD evoked by compound stimulation decreased. On the contrary, IPSP amplitude and PPD evoked by minimal stimulation remained unchanged. We conclude that two types of GABAergic terminals exist in the rat neostriatum, only one of which is regulated by GABAₐ receptors. However, the other class of terminals, not regulated by GABAₐ receptors, displays a much more pronounced PPD.

METHODS

INTRODUCTION

It has been suggested that synaptically released γ-amino-butyric acid (GABA) exerts a feedback control over its own release in the neostriatum through GABAₐ receptors (Calabresi et al. 1991). In line with this suggestion, the GABAₐ receptor agonist R(-)baclofen reduces inhibitory postsynaptic potentials (IPSPs) evoked in the presence of antagonists for ionotropic glutamatergic excitation in rat neostriatal medium spiny neurons (Calabresi et al. 1991; Nisenbaum et al. 1992; Seabrook et al. 1990, 1991). The reduction of IPSPs by baclofen is not accompanied by any detectable changes in input resistance or membrane potential (Calabresi et al. 1991; Nisenbaum et al. 1992, 1993; Seabrook et al. 1991). Also, a slow IPSP is not found in medium spiny neurons. In neurons of other brain areas, baclofen activates a postsynaptic potassium conductance (Gähwiler and Brown 1985; Newberry and Nicoll 1985; for a review see Misgeld et al. 1995). The neostriatum, therefore, is an interesting structure in which to study the involvement of presynaptic GABAₐ receptors in the control of GABA release.

Pharmacological analysis of the reduction of intrastriatally evoked IPSPs by GABAₐ receptor agonists revealed some evidence for the existence of two discrete populations of GABAergic fibers in the neostriatum, only one of them being regulated by GABAₐ receptors (Seabrook et al. 1991). Applying focal bipolar intrastriatal stimulation, Seabrook et al. (1991) evoked GABA-mediated IPSPs, the components of which exhibited a differential sensitivity to GABAₐ agonists. They suggested that the GABAₐ-agonist-insensitive synaptic potential originated from the recurrent collaterals of medium spiny neurons. GABAergic fibers different with respect to baclofen sensitivity have also been found to impinge on hippocampal CA3 neurons (Lambert and Wilson 1993, 1994). Stimulating single fibers (minimal stimulation) Lambert and Wilson (1993, 1994) provided direct evidence for the existence of GABAₐ-agonist-sensitive and GABAₐ-agonist-resistant terminals.

Adopting this technique, we provide in this study evidence for the existence of two populations of GABAergic fibers in the neostriatum. Only one of these populations is regulated by GABAₐ receptors. Furthermore, we find two distinct types of paired-pulse depression (PPD) mediated by the corresponding terminals: 1) a GABAₐ-receptor-dependent PPD and 2) a GABAₐ-receptor-independent PPD. GABAₐ-receptor-independent PPD is more pronounced than GABAₐ-receptor-dependent PPD.

Slice preparation

Neostriatal slices (200–300 μm) were prepared from Wistar rats (100–120 g) as reported previously from this laboratory (Misgeld et al. 1979). The standard saline for preincubation and superfusion of the slices in an interface chamber consisted of (in mM) 134 NaCl, 2 KCl (5 for preincubation, ≈1 h), 2 CaCl₂, 1.3 MgCl₂, 26 NaHCO₃, 1.25 KH₂PO₄, and 10 glucose, pH 7.4. The recording solution contained in addition the non-N-methyl-D-aspartate (non-NMDA) receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX, 10 μM) and the NMDA receptor antagonist CGP37849 (5 μM). For preincubation and experimental procedures slices were kept at a temperature of 36°C.

Materials

The drugs used were as follows: (+)bicuculline (Sigma, Diesenhofen, Germany) and CNQX (Tocris Cookson, Bristol, UK). The NMDA receptor antagonist CGP37849, the GABAₐ receptor antag-
onist CGP55845A, and the GABA<sub>B</sub> receptor agonist R (−)baclofen were kindly provided by Ciba-Geigy (Basel, Switzerland). Drugs were applied via the bath solution or, in a few cases, by adding a droplet of concentrated solution to the bath (“bolus application,” Müller et al. 1988).

**Electrophysiological recordings**

Glass microelectrodes were filled with 3 M KCl for intracellular recordings (resistance 30–100 MΩ). The microelectrode was connected to a preamplifier (Neuronda IR-283) with an active bridge circuit. Only cells with membrane potentials more negative than −60 mV were included in the study.

**Electrical stimulation**

Two different stimulation paradigms were applied to perform electrical stimulation within the neostriatum. Compound stimulation was applied by the use of bipolar stainless steel electrodes. Stimulus intensities were adjusted (duration 0.1 ms; 0.03 Hz) to evoke compound responses with gradually increasing amplitudes in the range of 5–30 mV. Minimal stimulation was performed with glass microelectrodes filled with 4 M NaCl. Stimulus intensities were selected to evoke “all-or-none” responses (0.5–5 mV).

Data were digitized with a CED 1401 interface and stored on hard disk (IBM-AT-compatible PC) for subsequent analysis.

Use-dependent depression at inhibitory synapses (PPD) was investigated by applying pairs of stimuli with the use of compound and minimal stimulation. PPD was determined by the ratio of the response to the second stimulus and the amplitude of the response to the first stimulus. When the rising phase of the second IPSP of a pair occurred during the decay phase of the first IPSP, the amplitude of the second response was measured after subtraction of an IPSP evoked by a single stimulus.

**RESULTS**

The results described in the present study are based on intracellular recordings from presumed medium spiny neurons (Misgeld et al. 1984). Postsynaptic potentials were evoked by intrastriatal stimulation in the presence of antagonists for ionotropic glutamatergic excitation, CNQX (10 μM) and CGP37849 (5 μM) (Rohrbacher et al. 1994). Two different stimulation paradigms were used: 1) minimal stimulation that activated a single or very few presynaptic elements (Edwards et al. 1990; Lambert and Wilson 1993; Mori et al. 1994) and 2) focal bipolar intrastriatal stimulation that activated the presynaptic network of fiber bundles and cells, referred to here as compound stimulation. Minimal stimulation was applied with the use of low-intensity electrical stimuli delivered through glass microelectrodes positioned at a distance within 100 μm of the recorded cell. Responses evoked by minimal stimulation displayed amplitude fluctuations that were independent of stimulus intensity within a defined range of stimulus strengths (Fig. 1C). Depending on stimulus intensity, response failures were more or less frequent (Fig. 1, A and C). Amplitudes of responses to minimal stimulation were in the same range as those of spontaneously occurring synaptic potentials (Fig. 1A). Responses were completely blocked by the GABA<sub>A</sub> receptor antagonist bicuculline (30 μM), indicating that they were IPSPs (n = 21). Responses evoked by compound stimulation displayed a graded increase of amplitudes with increasing stimulus intensity. Application of bicuculline (30 μM) strongly decreased the amplitude of the compound response (Fig. 1B1), whereas the IPSP evoked in the same cell by minimal stimulation was blocked (Fig. 1B2). A residual response remained even if slices were perfused for ≥1 h with high concentrations of GABA<sub>A</sub> (bicuculline and picrotoxin, 50 μM each) and glutamate receptor antagonists (n = 7), as also described by others (Rohrbacher et al. 1994; Seabrook et al. 1991). After such a long time, there is equilibration between drug concentrations in the bath and in the slice (Müller et al. 1988). Therefore the response to compound stimulation is mixed postsynaptic potential with its major part being mediated by GABA<sub>A</sub> receptors. It is unlikely that the residual response exclusively results from an activation of GABA<sub>B</sub> receptors by high GABA concentrations that could result from spillover of transmitter from neighbouring synapses (Clements 1996). In the presence of GABA<sub>B</sub> and glutamate receptor antagonists a postsynaptic potential can be evoked also by minimal stimulation (Radnikow et al. 1995).

**Modulation of IPSPs by GABA<sub>B</sub> Receptors**

The GABA<sub>B</sub> receptor agonist R (−)baclofen (1–20 μM), in a concentration-dependent and reversible manner, reduced compound response amplitudes (Fig. 2) (Calabresi et al. 1991; Nisenbaum et al. 1993; Seabrook et al. 1991), whereas IPSPs evoked by minimal stimulation were blocked in 13 of the 14 tested cells. Even at a concentration of 1 μM, responses to minimal stimulation were completely blocked, whereas compound responses were only reduced to 50% of the original amplitude in the same cells (n = 6, Fig. 2, A and C). However, in one cell R (−)baclofen (10 μM) had no effect on the response evoked by minimal stimulation, but strongly reduced the response evoked by compound stimulation. As reported by many other investigators, R (−)baclofen did not induce changes in the membrane potential or input resistance of the recorded cells (Calabresi et al. 1991; Nisenbaum et al. 1992, 1993; Seabrook et al. 1990, 1991). In the presence of the GABA<sub>B</sub> receptor antagonist CGP55845A (0.5 μM), R (−)baclofen (10 μM) had no effect either on the responses to compound or to minimal stimulation (n = 4).

Our data support and extend previously published reports (cf. introduction) that demonstrate that, in the neostriatum, activation of GABA<sub>B</sub> receptors suppresses evoked GABA<sub>A</sub>-receptor-mediated IPSPs by a presynaptic mechanism. The functional role suggested for presynaptic GABA<sub>B</sub> receptors is to exert a negative feedback control over GABA release (Calabresi et al. 1991). Such a hypothesis can be tested by paired-pulse stimulation (Davies et al. 1990). Paired-pulse stimulation was applied at interstimulus intervals ranging from 5 ms to 1 s. Responses evoked by compound stimulation displayed PPD at interstimulus intervals between 50 ms and 1 s (Fig. 3, A and B). Although PPD was found rather consistently with compound responses, individual pairs of responses occasionally showed variance, i.e., no PPD or even a slight facilitation. PPD, however, was always clearly evident if responses were averaged (2–5 traces).

Responses evoked by minimal stimulation displayed considerable variance in amplitude. This variance was to be expected because of the amplitude fluctuations characteristic
of responses to minimal stimulation and the occurrence of failures. PPD became obvious, however, if data were averaged (6–10 traces). Only pairs of responses in which neither the first nor the second response was a failure were averaged. All further investigations were based on averaged responses at an interstimulus interval of 300 ms (Fig. 4A). GABA_B receptors are expected to be activated at this interstimulus interval (Calabresi et al. 1991; Davies et al. 1991; Lambert and Wilson 1994; Otis and Mody 1992; Pitler and Alger 1994).

In slices that were perfused with control solution, PPD was found consistently at an interstimulus interval of 300 ms without a significant difference between responses evoked by compound or minimal stimulation (Fig. 4, A, C1, and C2). In another group of slices in which GABA_A receptors were blocked by perfusion with CGP55845A (0.5 μM) for ≈1 h, there was still PPD of compound responses (Fig. 4, B and C1). Responses evoked by minimal stimulation, in contrast, no longer showed PPD (Fig. 4C2). Application of CGP55845A reversed PPD of responses to minimal stimulation to a slight facilitation (Fig. 5).

Frequency-dependent modulation of IPSPs independent of GABA_B receptors

The blockade by CGP55845A of PPD elicited by minimal stimulation indicates that there is a GABA_A receptor-mediated component of PPD. Two observations were, however, not in accordance. 1) PPD of compound responses was not changed by CGP55845A. 2) In one neuron, R(−)-baclofen had no effect on the amplitude of the IPSP evoked by minimal stimulation, although it strongly reduced the compound response. To unravel these discrepancies, we decided to investigate paired-pulse stimulation under conditions under which GABA_A receptors were continuously activated by exogenous R(−)-baclofen. With the use of this approach, we
R(0) pound amplitudes increased to 175 ing prolonged perfusion with R(0) responses evoked by compound or minimal stimulation during were evoked after slices had been bathed for CGP55845A (0.5 m) response is the same. Responses to minimal stimulation, in contrast, display CGP55845A with R(0) C2. IPSPs evoked by minimal stimulation also displayed CGP55845A with R(0) much stronger for slices bathed in R(0) CGP55845A as it was for control slices, whereas it was to compound stimulation in the presence of CGP55845A (CGP). PPD of another subgroup of GABAergic terminals displayed paired-pulse facilitation rather than PPD. Another subgroup of GABAergic terminals displayed strong PPD (50% reduction). PPD in the neostriatum was intensified by R(−)baclofen, in contrast to the commonly observed reduction in PPD by the GABA B receptor agonist at terminals that have GABA B receptors.

FIG. 3. Paired-pulse depression (PPD) of compound responses. A: PPD of compound responses at interstimulus intervals of 50 ms (A1) and 100 ms (A2) (5 responses averaged; resting membrane potential = −82 mV). B: time course of PPD for postsynaptic potentials evoked by compound stimulation. Ratio of response amplitudes to 2nd stimulus over response amplitudes to 1st stimulus (s2/s1) are plotted against interstimulus interval. Each point represents the ratio s2/s1 (mean ± SE) observed in the number of cells indicated. Pronounced PPD was observed at an interstimulus interval of 300 ms.

had to consider the remote possibility of GABA B receptor desensitization, although we never observed a recovery of responses evoked by compound or minimal stimulation during prolonged perfusion with R(−)baclofen. Responses were evoked after slices had been bathed for ≥1 h in R(−)baclofen (10−20 μM) together with the antagonists for glutamatergic excitation. Compound responses were strongly reduced in amplitude by bicuculline (n = 3, Fig. 6A1), providing evidence that GABAergic postsynaptic potentials contributed to a considerable degree to the compound responses evoked in R(−)baclofen. In the same cells, bicuculline-sensitive IPSPs could be evoked by minimal stimulation (Fig. 6A2). Application of the GABA B receptor antagonist CGP55845A (0.5 μM) to slices incubated with R(−)baclofen (10 μM) for 1 h antagonized the reducing effect of R(−)baclofen on the compound response. Compound amplitudes increased to 175 ± 19% (mean ± SE) (n = 4) of the amplitudes before application of CGP55845A (Fig. 6B), providing evidence that GABA B receptors were indeed continuously activated. This was also suggested by the finding that PPD of compound responses was the same for slices continuously bathed in R(−)baclofen and CGP55845A as it was for control slices, whereas it was much stronger for slices bathed in R(−)baclofen (Fig. 4C1).

When paired-pulse responses in the presence of the fibers activated under control conditions. Corroborating this suggestion, addition of CGP55845A to R(−)baclofen produced an increase in response amplitude and a decrease of PPD for the compound response (n = 3). In the same cells, CGP55845A did not change amplitudes and PPD of responses to minimal stimulation (Fig. 7), indicating that the stimulated fibers did not carry GABA B receptors.

FIG. 4. PPD of responses to compound and minimal stimulation under different pharmacological conditions at an interstimulus interval of 300 ms, demonstrating a GABA B-receptor-dependent and a GABA B-receptor-independent PPD. A: PPD of responses to compound stimulation in control solution (resting membrane potential = −85 mV; average of 3 traces). Numbers in parentheses: ratio s2/s1. B: PPD of responses of another cell to compound stimulation in the presence of CGP55845A (CGP). PPD of compound responses is similar to that observed in control (resting membrane potential = −86 mV; average of 2 traces). Numbers in parentheses: ratio s2/s1. C: quantitative comparison of PPD characteristics under different pharmacological conditions displayed by compound responses (C1) and responses to minimal stimulation (C2). GABA B-receptor-independent PPD in the presence of R(−)baclofen (BAC) is significantly stronger than in control for both responses to compound and to minimal stimulation. In control (CON), in the presence of CGP55845A, and in the presence of CGP55845A with R(−)baclofen (CGP+BAC), PPD of compound responses is the same. Responses to minimal stimulation, in contrast, display a slight facilitation (C2) in CGP55845A. Bars: ratio s2/s1 (mean ± SE). Black bars: significant differences from PPD in control (P ≤ 0.05).

DISCUSSION

Our results demonstrate 1) the existence of two populations of GABAergic fibers, with only one of them being regulated by GABA B receptors, and 2) the existence of two mechanisms of use-dependent depression (PPD) of inhibitory synaptic transmission in the rat neostriatum, one being GABA B receptor dependent, the other GABA B receptor independent.

The evidence that some GABAergic inhibitory fibers in the neostriatum do not have GABA B receptors was as follows. 1) Minimal intrastriatal stimulation evoked IPSPs, some of which were sensitive and some insensitive to blockade by R(−)baclofen. 2) Different mechanisms of PPD could be discriminated. In control slices, there was weak PPD (20% reduction). In slices in which GABA B receptors were blocked by the high-affinity antagonist CGP55845A, a subgroup of GABAergic terminals displayed paired-pulse facilitation rather than PPD.
FIG. 5. Effect of perfusion with CGP55845A on PPD of responses to minimal stimulation. A: responses evoked by minimal stimulation in control solution (A1) and during perfusion with CGP55845A (0.5 μM, A2) in the same cell. CGP55845A reversed PPD to paired-pulse facilitation (resting membrane potential = −79 mV; average of 8 traces). Numbers in parentheses: ratio s2/s1. B: effect of CGP55845A on the ratio s2/s1. Second IPSP was depressed or facilitated in individual trials. During perfusion with CGP55845A, the occurrence and degree of facilitation increased compared with control.

Results were obtained with the use of two stimulation paradigms, minimal stimulation and compound stimulation, i.e., focal bipolar intrastriatal stimulation. Minimal stimulation (Edwards et al. 1990; Lambert and Wilson 1993; Mori et al. 1994) as used in the present study has several advantages in comparison with compound stimulation. The advantages were decisive for the conclusions drawn in the present study. With the use of minimal stimulation we could reliably evoke monosynaptic IPSPs, whereas compound stimulation elicited a mixed response. The activation of a single fiber or only a few fibers allowed a comparison of responses obtained in different slices maintained under different pharmacological conditions, which is by far more difficult if a changing mixture of network elements would be activated by compound stimulation. During compound stimulation, spillover of transmitter from densely packed activated synapses could have reduced the speed of clearance of transmitter from the cleft and enhanced peak postsynaptic receptor occupancy (Clements 1996). These factors could obscure the role of GABA_B receptors in frequency-dependent modulation of GABAergic transmission.

R(−)baclofen-sensitive and -insensitive GABAergic terminals

In slices continuously exposed to R(−)baclofen, IPSPs could be evoked by minimal stimulation in an all-or-none fashion. In control solution, however, all-or-none IPSPs evoked by minimal stimulation were blocked by R(−)baclofen. Therefore the IPSPs evoked by minimal stimulation in the presence of R(−)baclofen must originate from GABAergic terminals insensitive to R(−)baclofen. In control, we could activate R(−)baclofen-insensitive terminals only in one case, suggesting that R(−)baclofen-sensitive terminals by far outnumber R(−)baclofen-insensitive ones. The one example is, however, important, because it indicates that the ineffectiveness of R(−)baclofen during prolonged exposure was not due to GABA_B receptor desensitization but to the fact that we could stimulate R(−)baclofen-insensitive fibers more successfully in the presence than in the absence of R(−)baclofen. GABA_B-receptor-mediated effects, if they desensitize at all, desensitize only very slowly, a property characteristic for most G protein-coupled receptors as opposed to transmitter-regulated ion channels (for a review of the literature see Misgeld et al. 1995). In fact, although we did not observe a fading of the effects of R(−)baclofen with prolonged exposure, we could show by the use of the specific antagonist that, in R(−)baclofen, GABA_B receptors were continuously activated.

GABA_B-receptor-dependent and GABA_B-receptor-independent PPD

We could distinguish between two types of PPD. Under control conditions, responses evoked by minimal stimulation...
single-fiber stimulated inhibitory synapses between hippocampal cells in dissociated culture (Wilcox and Dichter 1994; Yoon and Rothman 1991) and glutamatergic synapses in the neostriatum (Mori et al. 1994). Pronounced GABA$_B$-receptor-dependent PPD has been described in many studies on compound responses (Davies et al. 1990, 1991; Deisz and Prince 1989; Mott and Lewis 1991; Mott et al. 1993; Otis and Mody 1992), which might indicate that activation of several inhibitory fibers is required for this form of PPD to be prominent (Lambert and Wilson 1994).

**Role of PPD in inhibition in the neostriatal network**

Our data on IPSPs evoked by minimal stimulation suggest that the majority of GABAergic fibers in the neostriatum is regulated by GABA$_B$ receptors. These fibers may be recurrent collaterals of medium spiny neurons (Fig. 8). Häusser and Yung (1994) describe an IPSP in substantia nigra neurons that was evoked by stimulation of the striatonigral pathway and inhibited by R(−)baclofen. These fibers generally did not display PPD but rather facilitation in the presence of the GABA$_B$ receptor antagonist CGP35348. The fibers of the striatonigral pathway originate from medium spiny neurons and form a plexus of axon collaterals within the neostriatum. Assuming that terminals of the same axons in the neostriatum also display the same PPD characteristics as those in substantia nigra, it is tempting to conclude that the neostriatal fibers inhibited by GABA$_B$ receptors belong to the same axons and thus come from medium spiny projecting neurons. However, there is no evidence that a principle of that kind really does exist. Indeed, there are reports in the literature that are not easily explained by our proposal.

Jaeger et al. (1994) suggest that synaptic inhibition between medium spiny neurons is weak or nonexistent in the rat neostriatum. On the other hand, considering that medium spiny neurons make up 95% of all striatal neurons and that medium spiny neuron axons form collaterals within the neostriatum, which is independent of GABA$_B$ receptors. The latter PPD is even more pronounced than GABA$_B$-receptor-dependent PPD. An important aspect of GABA$_B$-receptor-independent PPD seems to be its dependence on the amount of transmitter released in response to the first action potential (Wilcox and Dichter 1994). GABA$_B$-receptor-independent PPD has been described for a number of peripheral and central synapses, including the neuromuscular junction (Del Castillo and Katz 1954; Thies 1965) and inhibitory synapses on the goldfish Mauthner cell (Korn et al. 1984). It was even observed at the hippocampus...
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striatum (Kawaguchi et al. 1989; Kemp and Powell 1971; Preston et al. 1980; Somogyi et al. 1981), these axon collaterals may outnumber all other terminals of intrinsic origin and may be stimulated most frequently if a minimal stimulation protocol is used. Seabrook et al. (1991), studying the concentration requirements of the reduction by (+)-baclofen of IPSPs evoked in the neostriatum by compound stimulation, also concluded that GABAergic fibers in the rat neostriatum are heterogenous in that some have and some do not have GABA_A receptors. Waldmeier et al. (1989) reported that GABA release from substantia nigra is insensitive to GABA_A receptor agonists. Therefore Seabrook et al. (1991) concluded that GABAergic fibers without GABA_A receptors originated from medium spiny neurons under the assumption that properties of terminals originating from medium spiny neurons are identical in neostriatum and substantia nigra. However, there is conflicting evidence from GABA release studies (Giralt et al. 1990) for the presence of presynaptic GABA_A autoreceptors on GABAergic terminals in the substantia nigra.

In conclusion, our data present clear evidence that GABAergic fibers in the neostriatum are heterogenous in terms of the presence or absence of GABA_A autoreceptors. The fibers are also heterogenous with respect to PPD, which is more pronounced in fibers not regulated by GABA_A autoreceptors. We have only indirect evidence as to the origin of these different fibers. We suggest that GABAergic fibers regulated by presynaptic GABA_A autoreceptors originate from medium spiny neurons and fibers exhibiting GABA_A receptor-independent PPD originate from inhibitory interneurons (Fig. 8). Both neuronal types are excised from cortical origin. Repetitive discharge of cortical neurons (Plenz and Aertsen 1996a,b) could result in an enhancement of “on-line” outflow inhibition as opposed to intrinsic neostriatal inhibition and collateral inhibition.

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