J Neural Transm (1992) [Suppl] 38: 65–89

Behavioural pharmacology of glutamate in the basal ganglia

W. J. Schmidt, M. Bubser, and **W. Hauber***

Neuropharmacology Division, Zoological Institute, University of Tübingen, Federal Republic of Germany

Summary. In Parkinson's disease the dopaminergic inhibition – mediated by DA2 receptors in the striatum – is reduced. Therefore glutamatergic excitation predominates in the antero-dorsal striatum. In turn the glutamatergic neurons of the subthalamic nucleus become disinhibited. Antagonists of the NMDA-subtype of glutamate receptors injected locally into the glutamatergically innervated nuclei or competitive and non-competitive NMDA-antagonists administered systemically, counteract parkinsonian symptoms in animals.

Introduction**

It has taken a long time from the first demonstration of the excitatory actions of GLU in 1958, to its general acceptance as a centrally acting neurotransmitter (for review see Watkins, 1988). Today, GLU is considered to be the main transmitter mediating synaptic excitation in the mammalian brain. GLU is the transmitter of several subcortical projections, of some cortical afferents and of intracortical connections. Most probably all corticofugal projections use GLU as their transmitter. Thus, also the basal ganglia receive massive glutamatergic afferents from the cerebral cortex (Fonnum, 1984).

Functional anatomy of the basal ganglia

There is growing evidence for the existence of loops from the cortex via the striatum, the pallidum and the thalamus back to the cortex (Alexander, 1986). These loops are considered in the present context as "main loops". Two "side loops" exist that may influence information processing through the main loops: First, a loop from the striatum to the SNc, back to the striatum using

* Present address: Department of Animal Physiology, University of Stuttgart, Pfaffenwaldring 57, D-W-7000 Stuttgart 80, Federal Republic of Germany
** Abbreviation and drugs see page 89

GABA and DA as transmitters and second, a loop from the GPe to the STN back to the GPi/SNr using GABA and GLU as transmitters (Fig. 1).

The striatum is the main input station of the basal ganglia. Previously, the striatum has been considered as a funnel receiving converging and overlapping projections from the cortex. Nowadays it is thought that the somatosensory cortices preferentially innervate the putamen while the association cortices innervate the nucleus caudatus. These cortical inputs are arranged in such a way that a specific cortical area projects upon a specific (associated) area of the putamen or nucleus caudatus respectively. In both striatal structures the inputs remain segregated and, from preliminary evidence, it has been suggested that this segregation may be preserved through the whole main loops. The striatum and its ventral extension, the nucleus accumbens, receive glutamatergic afferents also from the hippocampus and amygdala (Walaas, 1981).

Most important for our view about segregated information processing through the main loops and possible integration is the finding of Haber et al. (1985) who showed the existence of a direct projection from the GPe to the reticular nucleus of the thalamus which projects to other thalamic nuclei but not to the cortex. These various connections may represent the substrate by which basal ganglia outputs inhibit or disinhibit thalamic activity and that of thalamocortical afferent neurons, which are thought to be GLUergic.

The striatal output neurons (medium sized spiny I neurons) are GABA-ergic: They project to the GPe and to the SNr/GPi in the course of the main

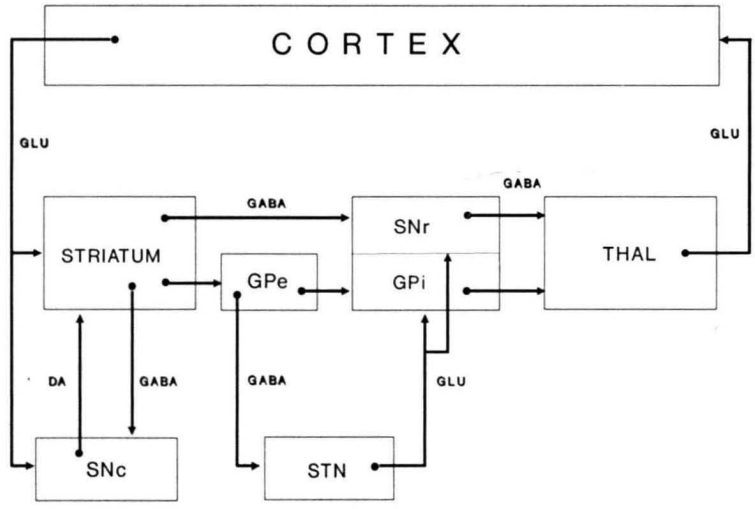

Fig. 1. Schematic diagram of the circuitry and neurotransmitters of the basal ganglia. *GPe* globus pallidus external segment; *GPi* globus pallidus internal segment; *SNr* substantia nigra pars reticulata; *SNc* substantia nigra pars compacta; *STN* subthalamic nucleus; *THAL* thalamus; *DA* dopamine; *GABA* gamma-aminobutyric acid; *GLU* L-glutamic acid

loops and in a side loop to the SNc. The excitatory GLUergic input from the cortex activates the inhibitory striatofugal GABAergic neurons. Via a direct pathway through the GPi/SNr, such a cortical input to the striatum activates the thalamic relay nuclei. But via an indirect pathway through GPe, STN, GPi/SNr a cortical input inhibits the thalamic relay nuclei (Fig. 1).

Within the striatum, the DAergic neurons of the side loop ascending from the SNc are both inhibitory and excitatory: DA activates through D1-receptors those GABAergic output neurons that use substance P as cotransmitter and that project directly to the SNc or to the GPi/SNr. But DA inhibits through D2-receptors the GABAergic neurons of the indirect pathway that use enkephalins as cotransmitters and project to the GPe (Gerfen et al., 1990). Thus, in contrast to a GLUergic input, DA release within the striatum results in a uniform effect on thalamic relay nuclei: DA – via D2-receptors – inhibits the striatofugal output neurons of the indirect pathway but excites – via D1-receptors – striatal output neurons of the direct pathway. Therefore, in the striatum exists a balance between GLU that activates, and DA that inhibits the GABAergic neurons of the indirect pathway.

Glutamate receptors in the basal ganglia

GLU binds to at least three different receptor types: Two are ionotropic and labelled according to their preferred agonists, i.e. the NMDA – and the AMPA receptor and one is a metabotropic G-protein coupled receptor.

Among the basal ganglia nuclei, the striatum has the highest density of all glutamate receptors (Albin et al., 1992). The density of NMDA receptors in the striatum of rats (Monaghan and Cotman, 1985; Albin et al., 1992) and in the nucleus caudatus and putamen of monkeys (Young et al., 1990) is approximately one half of the density of NMDA receptors found in the hippocampus where the highest densities occur (Young et al., 1990) and about ten fold higher than in the other nuclei of the basal ganglia.

AMPA and metabotropic receptor densities as shown by quisqualate binding, are approximately 30% lower in the striatum than in the hippocampus (Young et al., 1990). AMPA receptor density in the striatum is approximatly 4 fold higher while the density of the metabotropic receptor is only about 2 fold higher than in other basal ganglia nuclei (Albin et al., 1992).

Behavioural pharmacology

Dysfunctions of the transmitter balance within all basal ganglia loops cause motor and cognitive deficiencies in animals and men. In the following, the dependence of several behavioural variables from the DA–GLU balance in the basal ganglia will be considered.

Catalepsy

Catalepsy in the rat is a state of postural immobility (akinesia), muscular rigidity (rigor) and tremor of the limbs due to an experimentally induced DAergic deficiency (Sanberg et al., 1988; Colpaert, 1987). Catalepsy is a condition in which those systems of the brain, involved in the initiation of voluntary movements are inoperative but in which the animal is awake and those systems of the brain involved in reflexive control, static postural support and equilibrium are operative (Schallert and Teitelbaum, 1981). Although the internally generated (arbitrary) initiation of behaviour is inoperative, strong external stimuli such as tail pinch, cold water (Ungerstedt, 1974) or key stimuli adequate to activate innate releasing mechanisms (Schmidt, 1984; Wegener et al., 1988) can activate an otherwise cataleptic animal.

Catalepsy is induced by all treatments that reduce the activity of the mesostriatal and mesolimbic DAergic neurons, for example by reserpine (Colpaert, 1987), α-MPT or by blockade of postsynaptic DA receptors by D1- or D2-receptor-antagonists (Ögren and Fuxe, 1988; for review see Schultz, 1982). As shown by Sanberg (1980), postsynaptic, not presynaptic DA receptors mediate neuroleptic-induced catalepsy. Local destruction of DA cells in the SNc with 6-OHDA or MPP^+ or the destruction of the ascending DA neurons to the striatum also induce catalepsy. However, lesions of the dopaminergic terminals within the prefrontal cortex do not induce catalepsy but rather have stimulating effect on behaviour, i.e. induction of locomotion (Bubser and Schmidt, 1990).

Recently adenosine A2 agonists have been reported to induce catalepsy in the rat. This was explained by the existence of a central A2/D2 receptor interaction, i.e. by the A2-induced inhibition of D2 transmission (Ferré et al., 1991). GLU excites and DA inhibits the striatal output neurons of the indirect pathway via the GPe. Given that DA and GLU via the NMDA receptor have opposite behavioural effects in the striatum (Schmidt, 1986a; Girault et al., 1990) administration of NMDA would be expected to induce catalepsy. In fact, NMDA given systemically (7.5, 15, 30 mg/kg i.p.) or locally into the striatum (0.5 and 1 μg) (Schmidt and Bury, 1988) reduced all behavioural activities, but it did not induce catalepsy. However, when NMDA (40 mg/kg i.p.) was given in combination with haloperidol, it potentiated the cataleptogenic effects of haloperidol (Mehta and Ticku, 1990).

Reversal of catalepsy

Systemic administration of drugs

A treatment is considered to be anticataleptic if I) it reduces the time span from placement of the animal into an unusual posture until the first active movement to correct this posture and II) if it does not disturb reflexive control, static postural support and equilibrium.

Catalepsy due to DA-deficiency is reversed by indirect and direct DA-agonists: L-DOPA, amphetamine and other treatments that enhance presynaptic DA release are effective and postsynaptic D2-agonists such as bromocriptine as well. An anticataleptic effect of a D1-agonist has not unequivocally been shown as yet (for review see Sanberg et al., 1988; Wachtel, 1991).

Anticholinergic drugs antagonize catalepsy as well (Hillegaart and Ahlenius, 1987).

Because of the opposite effects of DA and GLU on akinesia and rigidity (Schmidt, 1986a), antagonists of glutamatergic transmission should be able to compensate for the behavioural effects of reduced DA activity and thus may have anticataleptic effects. In fact, this has been shown at first for dizocilpine (MK-801), a substance that blocks the NMDA receptor gated ion channel when in its open state. Dose-dependendly (0.08, 0.16, 0.33 mg/kg i.p.) dizocilpine reversed haloperidol (0.5 mg/kg i.p.) – induced catalepsy (Schmidt and Bubser, 1989; Elliott et al., 1990). Mehta and Ticku (1990) confirmed this finding and additionally showed a potentiation of the anticataleptic effect of scopolamine and bromocriptine by dizocilpine. Dizocilpine also reversed catalepsy induced by the D1-antagonist SCH 23390 (Schmidt et al., 1991). The aminoadamantane memantine, used clinically in the treatment of spasticity and Parkinson's disease, has been shown to behave as a non-competitive NMDA-antagonist (Bormann, 1989; Kornhuber et al., 1989). Memantine antagonized catalepsy induced by neuroleptics or by DA-depletion with reserpine and α-MPT (Maj et al., 1974; Schmidt et al., 1991).

The blockade of the NMDA binding-sites by the competitive NMDA-antagonists CGP 37849, CGP 39551 and SDZ EAA 494 (Lowe et al., 1990) had anticataleptic effects as well (Kretschmer et al., 1992). Also allosteric modulation of the NMDA receptor via its glycine binding-site influences catalepsy: the glycine-antagonist 7-chlorokynurenic acid (given i.c.v.) antagonized haloperidol-induced catalepsy (Kretschmer and Schmidt, 1992). The glycine-agonist D-cycloserine (i.p.) did not affect catalepsy when given alone but it abolished the anticataleptic effect of the competitive NMDA-antagonists. The anticataleptic potency of dizocilpine was enhanced (Kretschmer et al., 1992). This latter finding may be explained by an increase in the opening rate of NMDA receptor gated ion channels where dizocilpine binds use-dependently (Wong et al., 1987).

There is less evidence about the involvement of non-NMDA receptors. The AMPA antagonists NBQX and GYKI 52466 did not change haloperidol-induced catalepsy (Zadow and Schmidt, 1992a).

Local administration of drugs

Striatum: Yoshida et al. (1991) investigated the involvement of the cortico-striatal glutamatergic projection in the induction of haloperidol-induced catalepsy. To this end they ablated the frontal cortex and injected various

glutamatergic drugs into the striatum. In accordance with previous studies done by Scatton et al. (1982) and Worms et al. (1985) it was shown that bilateral lesions of the frontal cortex markedly reduced the cataleptic effect of haloperidol. Further it was found that the selective blockade of NMDA receptors with AP-5 within the rostral striatum reduced catalepsy analogous to that produced by interruption of the cortical efferents. A non NMDA-antagonist was ineffective in this respect. NMDA locally injected into the striatum was able to restore haloperidol-induced catalepsy in frontally decorticated rats (Yoshida et al., 1991).

The critical involvement of striatal NMDA receptors is further emphasized by lesion studies with the neurotoxin quinolinic acid. Quinolinic acid acts preferentially via NMDA receptors and destroys spiny I neurons; striatal interneurons en passage are spared. Such lesions in the striatum also prevent the induction of catalepsy (Schmidt and Bischoff, 1988; Calderon et al., 1988). Quinolinic acid lesions of the lateral striatum most effectively prevent catalepsy while lesions of the medial striatum rather affect cognitive processes (Hauber, 1990a). This latter finding nicely corroborates the view of segregated loops mediating different aspects of behaviour.

Other basal ganglia nuclei: Taken together, the results reported so far strongly support the view that the striatum (lateral part) is an essential constituent of a loop mediating catalepsy (Hauber, 1990a). Because only in the indirect pathway DA and GLU (via the NMDA receptor) have opposite roles, this pathway (from the striatum to the GPe, STN, THAL) may represent the neuroanatomical substrate of this loop. Direct evidence for the involvement of this pathway in akinesia and rigidity derives from experiments with MPTP-treated monkeys: The MPTP-induced loss of striatal DA leads to overactivity of the striato-GPe neurons as shown by binding studies (Robertson et al., 1990a), by in situ hybridisation (Augood et al., 1989) and microdialysis experiments (Robertson et al., 1990b). Such overactivity inhibits the GPe and disinhibits the STN in the side loop (DeLong, 1990; Aziz et al., 1991) which in turn acitvates the GPi/SNr (Fig. 1). Lesions of the STN or AMPA receptor blockade with NBQX in monkeys antagonized MPTP-induced akinesia and rigidity (Aziz et al., 1991; Greenamyre et al., 1991). The NMDA-antagonist CPP reduced rigidity also in monoamine-depleted rats when locally injected into the STN or GPi/SNr (Klockgether and Turski, 1990). Quinolinic acid lesions of the entopeduncular nucleus of the rat, the homologue of the GPi, which is overactive in DA-deficiency states, did not change catalepsy. However reserpine and haloperidol-induced catalepsy was reduced, if additionally AMPA receptors were blocked by systemically administered GYKI 52466 (Zadow and Schmidt, 1992b).

GLUergic transmission is also operative in the other side loop through the SNc: The SNc receives a cortical GLUergic input (Fig. 1) (Carter, 1982; Kornhuber, 1984; Ottersen and Storm-Mathisen, 1986). Electrical stimulation

of the cortex (Nieoullon et al., 1978) and iontophoretically administered GLU enhance the release of DA in the SNc which may inhibit nigrostriatal DAergic neurons by autoreceptors (Araneda and Bustos, 1989). Blockade of NMDA receptors in the SNc with locally administered AP-5 (5 nmol/0.5 µl) reduced haloperidol-induced catalepsy (Schuster and Schmidt, 1988; Schuster, 1990).

Locomotion and stereotypy

The locomotor activity of an animal is influenced by various motivational states and environmental variables. Drugs belonging to diverse classes with different mechanisms of action change locomotor activity. However there is unequivocal evidence that DA in the basal ganglia is critically involved in locomotor control: Drugs that facilitate DAergic transmission induce a syndrome characterized by increased locomotion and stereotyped behaviours (Randrup and Munkvad, 1967). Stereotypy can be defined as the performance of an invariant sequence of movements in a repetitive manner (Fray et al., 1980) not controlled by external stimuli. Stereotypy is species-specific. In the rat it is manifested as continuous running, rearing and sniffing at low to medium doses of DA-agonists, as continuous sniffing in one location, gnawing, biting, licking at high doses. At extremely high doses the animal ceases to move although it is highly alert (for review see Lyon and Robbins, 1975).

DAergic antagonists reduce spontaneous locomotor activity of rats and antagonize DA-agonist-induced hyperlocomotion and stereotypy. This antagonism is one of the most widely used screening procedure for neuroleptic drugs. Classical neuroleptics, such as haloperidol antagonize stereotypy and locomotion while the atypical ones, for example clozapine, do not antagonize stereotypy but specifically locomotion (Ljungberg and Ungerstedt, 1978, 1985; Robertson and MacDonald, 1984). Thus antagonism of DA-induced locomotion is thought to correlate with the antipsychotic potency of neuroleptic drugs.

As with catalepsy, DA and GLU appear to have opposite effects also on locomotion and stereotypy: The non-competitive NMDA-antagonist dizocilpine strongly stimulated locomotion and behaved like amphetamine in the rotational model (Clineschmidt et al., 1982), additionally sniffing was enhanced (Tiedtke et al., 1990). However, in contrast to DA-agonists the focused stereotypies e.g. sniffing in one location and the oral stereotypies e.g. gnawing, biting, licking did not occur under dizocilpine. Neuroleptic drugs antagonized dizocilpine-induced hyperlocomotion, rotational behaviour and sniffing (Clineschmidt et al., 1982). Interestingly, also the atypical neuroleptic clozapine antagonized the dizocilpine effects (Tiedtke et al., 1990).

The competitive NMDA-antagonists did not induce such a pronounced stimulation of locomotion and stereotypy, in fact, low and medium doses of SDZ EAA 494 (Svensson et al., 1991) CGP 37849 and CGP 39551 did not enhance locomotion of rats 45 min after drug administration; sniffing was slightly enhanced (Kretschmer et al., 1992). However when SDZ EAA 494

was given at higher doses (10, 20, 40 mg/kg) to mice and the observation period was extended, then between 60 and 160 min after drug administration locomotor stimulation was observed (Svensson et al., 1991).

Reversal of DA-deficiency-induced locomotion – and sniffing deficit

Systemic administration of drugs

It is well known that DA-agonists restore locomotor activity in DA-deficient animals and parkinsonian patients (for review see Wachtel, 1991) confirming the view that DA plays the most crucial role in the induction of locomotion. Thus, it was a most important finding that in monoamine depleted mice, i.e. in the complete absence of DA, the non-competitive NMDA-antagonist dizocilpine produced marked locomotor stimulation (Carlsson and Carlsson, 1989, 1990, but see also Goodwin et al., 1992) as did the competitive NMDA-antagonist SDZ EAA 494 (Kannari and Markstein, 1991). Also in monoamine depleted rats (Schmidt et al., 1990b) or in rats pretreated with haloperidol, dizocilpine stimulated locomotion but CGP 37849 (2 and 4 mg/kg, 45 min before test) was ineffective in this respect (Kretschmer et al., 1992). Additionally when coinjected with L-DOPA, competitive (CPP) and non-competitive (dizocilpine) NMDA-antagonists have been shown to potentiate the ability of L-DOPA to restore locomotion in monoamine depleted rats (Klockgether and Turski, 1990). Goodwin et al. (1992) reported that dizocilpine potentiates D1- but not D2-dependent locomotion.

Taken together, from these findings it appears that GLU potently depresses locomotion while blockade of NMDA receptors seems to be a general principle by which locomotion is enhanced. The non-competitive NMDA-antagonists were found to be more potent in this respect than the competitive ones (Schmidt et al., 1991). The AMPA-antagonist NBQX stimulated locomotor activity in reserpine-treated rats and MPTP-treated monkeys when given alone (Klockgether et al., 1991) or when coadministered with a threshold dose of L-DOPA (Löschmann et al., 1991).

Sniffing reduced by DA-deficiency, was restored by DA-agonists (Kelly et al., 1975) as well as by NMDA-antagonists (Tiedtke et al., 1990). As with locomotion, the non-competitive NMDA-antagonists were much more potent than the competitive antagonists. DCS, an agonist at the glycine binding site of the NMDA receptor was without any effect when given alone, when coadministered it potentiated dizocilpine-induced sniffing (Kretschmer et al., 1992).

Local administration of drugs

Striatum: DA in the nucleus accumbens, i.e. the ventral striatum, is involved in the control of locomotor activity: Local infusion of DA induced locomotion

(Costall et al., 1991; but see also Cools, 1986) and infusion of the neurotoxin 6-OHDA into the nucleus accumbens reduced locomotion in amphetamine-treated rats (Kelly et al., 1975). The dorsal striatum is involved in the control of sniffing and oral stereotypies since local 6-OHDA lesions reduced stereotypies in amphetamine-treated rats (Kelly et al., 1975). AP-5 injected into the nucleus accumbens induced strong locomotor stimulation (Bury, 1987).

Local infusion of the NMDA-antagonists AP-5 (Schmidt, 1986a), SDZ EAA 494 or dizocilpine (Imperato, 1990a) into the dorsal striatum enhanced sniffing in rats and induced locomotion. Infusion of NMDA had opposite effects, it reduced sniffing and locomotion in rats (Schmidt and Bury, 1988). In rats, unilaterally lesioned with 6-OHDA, dizocilpine increased contralateral turning induced by L-DOPA or by a D1-agonist but reduced turning induced by a D2-agonist (Morelli and DiChiara, 1990).

Thus, given systemically or locally, into the striatum or nucleus accumbens NMDA-antagonists induce a DA-like pattern of behavioural stimulation. The non-NMDA antagonists gamma-D-glutamyl-amino-methyl-sulphonic acid and glutamic-acid-diethyl-ester had not effects (Schmidt, 1986b).

Other basal ganglia nuclei: According to the proposed function of the indirect pathway (striatum, GPe, STN, GPi/SNr; see above) this pathway is also involved in locomotion. DA deficiency-induced excitation of STN-neurons associated with locomotor hypoactivity can be reversed by lesion of the STN (DeLong, 1990; Aziz et al., 1991) or by blockade of NMDA and AMPA receptors in the STN or GPi/SNr (Klockgether and Turski, 1990; Klockgether et al., 1991).

Movement initiation and execution

Inactivation of central DA neurotransmission by DA receptor-antagonists or midbrain neurotoxin lesion produces – as already described – catalepsy in rats. Besides, systemic administration of neuroleptics induces motor impairments in a variety of tasks, for instance a disruption of active avoidance responding (e.g. Fibiger et al., 1975; Spirduso et al., 1981), an impairement of reaction time performance (Amalric and Koob, 1987) or disturbances of operant responding in lever release tasks (Fowler et al., 1984, 1986; Skjoldager and Fowler, 1988). These different behavioural impairments are thought to be predominantly due to the animals inability to initiate motor behaviour, thus suggesting a dopaminergic involvement in the initiation of voluntary movements.

In order to get further insight into the role of dopamine in the control of initiation and execution of motor behaviour, we developed a novel simple reaction time task for rats. This task demands rapid initiation of locomotion in response to a stimulus in order to receive a food reward. Briefly, a modified runway was used which consisted of a start box and a runway terminating in a

goal box. A trained, gradually food deprived rat was placed into the start box with the face to the closed guillotine door blocking the entrance to the runway. After a variable delay, the stimulus signalled the simultaneous opening of the front door. In response to the stimulus, a rat initiated locomotion and moved through the runway to the goal box to get a food reward. The transition from stance to locomotion was recorded by means of a photoelectronic switch situated in front of the start box and a force platform mounted below the start box. The following measures can be taken from each trial: reaction time (latency between stimulus presentation and movement initiation), movement time (latency between movement initiation and leaving of the start box) and the initial acceleration (quantified by the rate of force development and peak force of the accelerative force) (Hauber, 1990b).

Neuroleptic-induced akinesia and bradykinesia

Systemic administration of haloperidol (0.15, 0.3 mg/kg, i.p.) induced specific impairments of movement initiation and execution in this paradigm: I) a delayed initiation of locomotion (termed here as akinesia) as measured by an increase of reaction time and II) a slowed movement execution (termed here as bradykinesia) as measured by an increase of movement time and a decrease of initial acceleration (Hauber and Schmidt, 1990; Schmidt et al., 1991).

The haloperidol-induced increase of reaction time corresponds well to the neuroleptic-induced prolongation of response latencies obtained in other rodent paradigms (Amalric and Koob, 1987; Spirduso et al., 1981). These findings further support the concept of a DA involvement in the initiation of movement. The haloperidol-induced slowing of movement execution and decrease of the dynamic indices of a movement is also consistent with earlier observations of neuroleptic actions on movement time and force production (e.g. Fowler et al., 1986). In addition, deficits of force production are found in patients with Parkinson's disease (Stelmach and Worringham, 1988; Wierzbicka et al., 1991).

Thus, DA is not only a prerequisite for rapid initiation of a movement but also subserves the adequate regulation of force and time paramenters of a movement.

The neuroleptic-induced pattern of impairments observed in the task described here are reminiscent to akinesia and bradykinesia seen in parkinsonian patients. Thus the paradigm may be a useful model to investigate potential Parkinson drugs.

Reversal of neuroleptic-induced akinesia and bradykinesia

We further examined whether different non-competitive (dizocilpine, amantadine, memantine) and competitive (CGP 37849) NMDA-antagonists as well as a DA-agonist (bromocriptine) are able to reverse haloperidol-induced akinesia and bradykinesia in this paradigm.

Single administration

First we investigated the effects of these compounds on movement initiation and execution when given alone, respectively. It was found that dizocilpine (0.08 mg/kg, i.p.), amantadine (44 mg/kg, i.p.), memantine (10 mg/kg, i.p.), CGP 37849 (4 mg/kg, i.p.) or bromocriptine (10 mg/kg, i.p.) caused no pronounced alterations of reaction time performance (only amphetamine (1 mg/kg, i.p.) induced a significant decrease of reaction time).

Regarding the effects on movement execution, marked differences were detected. Dizocilpine and – less potently – amantadine induced a mild increase of movement performance (decrease of movement time and/or increase of initial acceleration), memantine and – less potently – CGP 37849 produced a prominent decrease (increase of movement time and/or decrease of initial acceleration) of movement performance. The decrease of movement performance induced by the latter two substances seems to be due to their muscle relaxant properties. Bromocriptine also produced a slight decrease of movement performance (Hauber and Schmidt, 1990; Schmidt et al., 1991; Hauber, unpublished observations). The findings on movement execution are in line with the stimulatory effects on spontaneous motor activity shown for dizocilpine (Clineschmidt et al., 1982) and amantadine (Maj et al., 1974) and the CGP 37849-induced reduction of spontaneous locomotion (Kretschmer et al., 1992).

Coadministration with haloperidol

The increase in reaction time (akinesia) induced by a single administration of haloperidol (0.15 mg/kg, 0.3 mg/kg, i.p.) was antagonized by coadministration of dizocilpine (0.08 mg/kg, i.p.), CGP 37849 (4 mg/kg, i.p.) or bromocriptine (10 mg/kg, i.p.). The anti-akinetic effects of amantadine (44 mg/kg, i.p.) or memantine (10 mg/kg, i.p.) were less pronounced. These findings are constistent with the anti-cataleptic activity of dizocilpine (Schmidt and Bubser, 1989; Elliott et al., 1990; Mehta and Ticku, 1990), CGP 37849 (Kretschmer et al., 1992), bromocriptine (Colpaert, 1987; Boissier et al., 1980), amantadine (Maj et al., 1974) and memantine (Schmidt et al., 1991).

In contrast, haloperidol-induced slowing of movement execution (bradykinesia) was antagonized only by coadministration of dizocilpine or – less potently – by amantadine. Memantine, CGP 37849 or bromocriptine produced no anti-bradykinetic effects. (Hauber and Schmidt, 1990; Schmidt et al., 1991; Hauber, 1992). The lack of anti-bradykinetic effects of memantine and CGP 37849 could be explained by their marked muscle relaxant properties which can be already observed when given alone and – as in case of coadministration with haloperidol – these properties prevent a restoration of impaired movement performance. The absent anti-bradykinetic effect of bromocriptine is most probably due to the fact that stimulatory effects of

bromocriptine on locomotor activity are only prominent in mice, and stereotypies, competing with locomotor behaviour, are predominant in rats. Thus, the use of bromocriptine as a reference substance in this test is of limited value.

In conclusion, competitive and non-competitive NMDA antagonists have marked anti-akinetic effects. However, considerable differences exist in the anti-bradykinetic effects of these compounds. Provided that the paradigm used here represents a model of Parkinson's disease, these findings confirm that the use of NMDA-antagonists may be a novel strategy for the treatment of this disease. The differential anti-akinetic and anti-bradykinetic profiles of these NMDA antagonists may be an important criterion to assess their clinical potential.

Local administration of drugs and neurotoxins

Results from numerous studies support the hypothesis that nigrostriatal DA has an essential role in the initiation of motor acts. Depletion of DA in the striatum impaired reaction time performance of rats in operant tasks (Amalric and Koob, 1987; Spirduso et al., 1985) and in visual discrimination tasks (Carli et al., 1985; Brown and Robbins, 1989, 1991). Local striatal infusion of haloperidol but not of carbachol also delayed movement initiation (Amalric and Koob, 1987).

Since DA depletion in the nucleus accumbens did not impair reaction time performance (Amalric and Koob, 1987), the mesolimbic DA system seems not to be involved in reaction time processing. On the other hand 6-OHDA lesions of the medial prefrontal cortex produced a prolongation of reaction time of rats (Hauber et al., 1991). From these results one may conclude that not only nigrostriatal DA subserves rapid initiation of movements, but also cortical prefrontal DA contributes to intact movement initiation.

According to the parallel loop model of basal ganglia functions, medial "cognitive" and lateral sensorimotor region of the frontal cortex innervate medial and lateral regions of the rodent striatum. An important implication of this concept is that disruption at different points of the same loop should cause similar behavioural deficits. In fact, this has been confirmed in many studies (e.g. Divac and Öberg, 1979). For instance, we found that lesions of the prefrontal cortex or blockade of NMDA receptors by local infusion of AP-5 into the corresponding medial striatum induced similar learning impairments in a maze task (Hauber and Schmidt, 1989; Bubser and Schmidt, 1990; Bubser et al., 1991a). These results confirm the participation of the "cognitive" cortico-striatal loop in maze learning. Since lesions of the prefrontal cortex caused – as already described – an increase of reaction time we expected a similar impairment following lesions of the medial striatum. Indeed, it was found that quinolinic acid lesions in the medial striatum but not lateral striatum prolonged reaction time (Hauber et al., 1991). This result is in line with a

similar finding following ibotenic acid lesions in the medial or lateral region of the striatum (Brown and Robbins, 1989).

Taken together, a lesion within the cognitive loop at level of the medial striatum induced a delayed movement initiation. A disruption of the DAergic modulation of this loop at the level of the prefrontal cortex or the striatum produced similar deficits. Thus, the cognitive loop may process informations related to movement initiation. This hypothesis is in accordance with recent studies in primates and parkinsonian patients (Montgomery and Buchholz, 1991; Montgomery et al., 1991a, b) leading to the conclusion that the cognitive loop may be uniquely suited to assess the behavioural context necessary for the decision when to move and the motor loop may be uniquely suited to decide how to move (Montgomery et al., 1991a).

Biochemistry

Methods for analyzing dopaminergic functions

Until a decade ago, the biochemical analysis of drug effects on the function of DAergic systems was mainly restricted to the determination of DA, its precursors and its metabolites in post-mortem brain tissue. By these means only indirect estimates of DA function are gained (see Wood and Altar, 1988). The parameters measured include I) the rate of L-DOPA accumulation and the rate of disappearance of DA after inhibition of tyrosine hydroxylase or DOPA-decarboxylase (see Liljequist et al., 1991; Svensson et al., 1991), II) the content of the extracellularly formed DA metabolite 3-MT that is regarded as an index of DA release (Westerink, 1985; Wood and Altar, 1988; Heal et al., 1990), III) the content of DOPAC, a metabolite that is predominantly formed intraneuronally after re-uptake of released DA has taken place, and IV) the metabolite/transmitter ratios, e.g. DOPAC/DA and HVA/DA (Zigmond et al., 1990).

Recently, in-vivo techniques like voltammetry and intracerebral microdialysis have been developed, which enable neuroscientists to determine in awake animals the extracellular levels of neurotransmitters and their metabolites in response to pharmacological challenges (for reviews see DiChiara, 1990; Adams, 1990).

Dopamine deficiency in man: Parkinson's disease

In Parkinson's disease DA neurons of the midbrain (substantia nigra and ventral tegmental area) projecting to the striatum (caudate nucleus and putamen) and to cortical areas degenerate (see Birkmayer and Riederer, 1985; Jellinger, 1991). In addition to mesencephalic DA systems, noradrenergic,

serotonergic and peptidergic transmitter systems are also affected by Parkinson's disease, but to a lesser degree (Jellinger, 1991).

Due to DA neurodegeneration, the post-mortem tissue content of DA in the striatum decreases; concomittantly the HVA/DA ratio increases (Zigmond et al., 1990). Although surviving DA systems are able to compensate a certain amount of cell loss (see below), the amount of released DA finally becomes insufficient to maintain intact behavioural functions. Usually, clinical symptoms of Parkinson's disease are observed when tissue DA content in the caudate nucleus and putamen is reduced by approximately 80% (see Zigmond et al., 1990).

Pharmacologically-induced dopamine deficiency

Several pharmacological tools have been developed in order to mimick the pattern of neurodegeneration in Parkinson's disease in experimental animals. DAergic neurodegeneration can be produced by intracerebral injections of the catecholaminergic neurotoxin 6-OHDA (Breese and Traylor, 1971; Jonsson, 1983), by systemic injection of MPTP (Rose et al., 1989), which in the brain is converted by monoamine oxidase type B to the toxic molecule MPP^+ (Sayre, 1989), or by intracerebral injection of MPP^+ (Beresford et al., 1988). Each neurotoxin causes a rather selective destruction of DA neurons, resulting in a decrease of tissue DA content (Breese and Traylor, 1971; Schultz et al., 1989), but other monoaminergic systems are also affected (Russ et al., 1991; Santiago et al., 1991). Reductions of DA content are accompanied by a less pronounced decrease of DOPAC and thus by an increase of DOPAC/DA ratio (Robinson and Whishaw, 1988; Rose et al., 1989; Schultz et al., 1989; Zigmond et al., 1989). Furtheron, the firing rate of DAergic neurons increases (Zigmond et al., 1990). By these compensating mechanisms DA function – as assessed by behavioural and biochemical measures – is not compromised as long as the striatal tissue depletion of DA does not exceed about 80%; further increases of DA depletion produce behavioural deficits and lead to a gradual reduction of extracellular DA levels (Robinson et al., 1990). Depending on the extent of a lesion, either stimulated DA release alone (Robinson and Whishaw, 1988) or both stimulated and basal release of DA are reduced (Castaneda et al., 1990; Bean and Roth, 1991). In rats, dramatic reductions of interstitial DA only occur with depletion of striatal DA by more than 95% (Castaneda et al., 1990).

In contrast to neurotoxins that cause irreversible dysfunction of DAergic neurons, reserpine only destroys the presynaptic vesicles containing biogenic amines. Following administration of reserpine, brain DA content and the levels of the extracellular DA metabolite 3-MT decline rapidly, whereas the intracellular metabolites DOPAC and HVA increase (Westerink, 1985).

Inhibition of DA synthesis by blockade of the the rate-limiting enzyme – tyrosine hydroxylase – with α-MPT, also reduces DA release in a reversible fashion (Shimizu et al., 1990; Abraini et al., 1991).

NMDA-antagonists and dopaminergic functions

Behavioural studies indicate that spontaneous behaviour is differentially affected by competitive and non-competitive NMDA-antagonists (see above). In order to elucidate whether these effects are due to differential interactions with DA systems, we analyzed the effects that the non-competitive NMDA-antagonists dizocilpine and memantine and the competitive NMDA-antagonist CGP 39551 exert on locomotor activity in an open field and on DA synthesis and metabolism in the basal ganglia (striatum and nucleus accumbens).

Both dizocilpine (0.33 mg/kg) and memantine (20 mg/kg) induced locomotor hyperactivity and increased DOPAC/DA in the nucleus accumbens, but not in the striatum, whereas CGP 39551 (10 and 20 mg/kg) affected neither open field activity nor DA metabolism of the forebrain (Bubser et al., 1991; Keseberg et al., 1991). Several other authors have also reported a stimulation of subcortical and cortical DA metabolism by the non-competitive NMDA-antagonists PCP, ketamine and dizocilpine (Deutch et al., 1987; Rao et al., 1990a, b; Tanii et al., 1990; Irifune et al., 1991; Liljequist et al., 1991; Svensson et al., 1991). The lack of effect of competitive NMDA-antagonists (AP-5, AP-7, CGS-19755, CPP and SDZ EAA 494) on subcortical DA metabolism is also well established (Rao et al., 1990b, 1991; Svensson et al., 1991).

The pattern of activation described above is in accordance with the differential effects of competitive and non-competitive NMDA-antagonists on the firing pattern of midbrain DA neurons (French and Ceci, 1990; French et al., 1991) and on regional cerebral brain metabolism (Chapman et al., 1990; Clow et al., 1991; Tamminga et al., 1991).

Let us now consider, how the DA-releasing effects of NMDA-antagonists may be mediated. For quantitative reasons it is unlikely that NMDA-antagonists exert their DA-releasing effects via presynaptic mechanisms at DA terminals within the basal ganglia, since more than 90% of striatal NMDA receptors are located at postsynaptic sites (Greenamyre and Young, 1989, see below). However, there remain two sites – each within the side loop from the striatum to the substantia nigra – where NMDA-antagonists may exert their effects on DA functions: I) the DA cell groups of the midbrain and II) the GABAergic efferents of the striatum and nucleus accumbens.

E.g., it has been shown that blockade of NMDA receptors by dizocilpine increases firing rate of midbrain DA neurons (French and Ceci, 1990) and DA metabolism in DA terminal areas (Rao et al., 1990a). A second site of action seems to be located in the striatum and nucleus accumbens, since local infusion of NMDA-antagonists into these nuclei increased DA release (Imperato et al., 1990a, b). This effect may be due to reduced excitation of the striatonigral GABAergic feedback loop which results in a decrease of GABA release in the substantia nigra. Since intranigral GABA inhibits striatal DA release (Reid et al., 1990), reduced GABAergic activity in the substantia nigra may in turn enhance striatal DA release. In this respect it is interesting to note

that not only NMDA-antagonists, but also lesions of the prefrontal cortex which sends glutamatergic efferents to the striatum and the midbrain increase the firing rate of mesencephalic DA neurons (Ceci and French, 1989).

In conclusion, the data presented here imply that non-competitive NMDA-antagonists produce some of their behavioural effects by a DA-dependent mechanism, since they are able to increase DA activity. However, the effects of non-competitive NMDA-antagonists can not solely be due to an interaction with DA systems, since they induce locomotion even in reserpinized mice (Carlsson and Carlsson, 1989) and in rats with lesion of the mesolimbic DA system, high doses of NPC 12626, a competitive NMDA-antagonist, induce locomotion (French et al., 1991). Furtheron high doses of SDZ EAA 4949 also induce locomotion in intact animals without affecting DA activity (Svensson et al., 1991).

Glutamate-antagonists and Parkinson's disease

It is proposed that DA-deficiency that induces catalepsy, reduces locomotion and sniffing and that impairs movement-initiation and execution represents an animal model for parkinsonian symptoms. Pharmacological reversal of these deficits by GLU-antagonists may give some indications for possible future therapy of the disease.

The non-competitive NMDA-antagonist dizocilpine was found to be maximally active in all the above tests but already in the rat, undesirable effects are obvious. These are ataxias, short-term memory deficits (Bischoff and Tiedtke, 1992) as well as stereotyped locomotion and sniffing instead of exploratory behaviour.

Competitive NMDA-antagonists do not induce such pronounced ataxias. Amnesia is induced only by a much higher dose than necessary to relieve rigidity and there is no induction of stereotyped running (Bischoff and Tiedtke, 1992; Kretschmer et al., 1992). Allosteric manipulation of the NMDA receptor by the glycine binding site may eventually be a promising strategy if it turns out that the isosteric NMDA-antagonists have too powerful side effects.

Given systemically, blockers of AMPA receptors have locomotion inducing effects when coadministered with L-DOPA (Löschmann et al., 1991; Klockgether et al., 1991).

Thus, the multiple sites for pharmacological intervention in the GLUergic system may provide the basis for the development of drugs with the desired specificity against parkinsonian symptoms. Further, while under L-DOPA medication DA receptor densities decrease this would be not the case with GLU-antagonists. Additionally, in Parkinson's disease the DAergic system degenerates, the GLUergic does not: no changes in NMDA receptor affinity and density have been found in the striatum. Thus, striatal NMDA receptors remain intact which is required for potential therapeutic use of NMDA-antagonists (Holemans et al., 1991).

Acknowledgements

Thanks are given to the Deutsche Forschungsgemeinschaft for financial support (SFB 307), Ciba Geigy, Institute for Drug Research Budapest, Merz, Novo Nordisk, Sandoz for gifts of drugs and to E. Wacker for skilful technical assistance.

References

Abraini JH, Raharison L, Rostain JC (1991) Long-term depression in striatal dopamine release monitored by in vivo voltammetry in free moving rats. Brain Res 548: 256–259

Adams RN (1990) In vivo electrochemical measurements in the CNS. Prog Neurobiol 35: 297–311

Albin RL, Makowiec RL, Hollingsworth ZR, Dure IV LS, Penney JB, Young AB (1992) Excitatory amino acid binding sites in the basal ganglia of the rat: a quantitative autoradiographic study. Neuroscience 46: 35–48

Alexander GE (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neurosci 9: 357–381

Amalric M, Koob GF (1987) Depletion of dopamine in the caudate nucleus but not the nucleus accumbens impairs reaction-time performance in rats. J Neurosci 7: 2129–2134

Araneda R, Bustos G (1989) Modulation of dendritic release of dopamine by N-methyl-D-aspartate receptors in rat substantia nigra. J Neurochem 52: 962–970

Augood SJ, Emson PC, Mitchell IJ, Boyce S, Clarke CE, Crossman AR (1989) Cellular localisation of enkephalin gene expression in MPTP-treated cynomolgus monkeys. Mol Brain Res 6: 85–92

Aziz TZ, Peggs D, Sambrook MA, Crossman AR (1991) Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. Mov Disord 6: 288–292

Bean AJ, Roth RH (1991) Effects of haloperidol administration on in vivo extracellular dopamine in striatum and prefrontal cortex after partial dopamine lesions. Brain Res 549: 155–158

Beresford IJM, Davenport AP, Sirinathsinghji DJS, Hall MD, Hill RRG, Hughes J (1988) Experimental hemiparkinsonism in the rat following chronic unilateral infusion of MPP^+ into the nigrostriatal dopamine pathway. II. Differential localization of dopamine and cholecystokinin receptors. Neuroscience 27: 129–143

Birkmayer W, Riederer P (1985) Die Parkinson-Krankheit. Biochemie, Klinik, Therapie, 2. Aufl. Springer, Wien New York

Bischoff C, Tiedtke PI (1992) Competitive and non-competitive NMDA-receptor antagonists in spatial learning tasks. Eur J Pharmacol 213: 269–273

Boissier JR, Dumont C, Laurent J, Oberlander C (1980) Profil psychopharmacologique d'un novel agoniste dopaminergique, le RU 24213. Psychopharmacology 68: 15–23

Bormann J (1989) Memantine is a potent blocker of N-methyl-D-aspartate (NMDA) receptor channels. Eur J Pharmacol 166: 591–592

Breese GR, Traylor TD (1971) Depletion of brain noradrenaline and dopamine by 6-hydroxydopamine. Br J Pharmacol 42: 88–99

Brown VJ, Robbins TW (1989) Elementary processes of response selection mediated by distinct regions of the striatum. J Neurosci 9: 390–365

Brown VJ, Robbins TW (1991) Simple and choice reaction time performace following unilateral striatal dopamine depletion in the rat. Brain 114: 513–525

Bubser M, Schmidt WJ (1990) 6-Hydroxydopamine lesion of the rat prefrontal cortex increases locomotor activity, impairs acquisition of delayed alternation tasks, but does not affect uninterrupted tasks in the radial maze. Behav Brain Res 37: 157–168

Bubser M, Hauber W, Schmidt WJ (1991a) The contribution of the cortico-striatal "cognitive" loop to the acquisition of maze performance in rats. Eur J Neurosci [Suppl] 4: 253

Bubser M, Keseberg U, Notz P, Schmidt WJ (1991b) NMDA-antagonists and dopamine metabolism. In: Rollema H, Westerink BHC, Drijfhout WJ (eds) Monitoring molecules in neuroscience. Proceedings 5th Int Conf on in vivo methods, Noordwijkerhout 1991. University Centre for Pharmacy, Groningen, pp 317–320

Bury D (1987) Control of behaviour of the rat in the "open field" by striatal glutamate. Verh Dtsch Zool Ges 80: 305–306

Calderon SF, Sanberg PR, Norman AB (1988) Quinolinic acid lesions of rat striatum abolish D_1- and D_2-dopamine receptor-mediated catalepsy. Brain Res 450: 403–407

Carli M, Evenden JL Robbins TW (1985) Depletion of unilateral striatal dopamine impairs initiation of contralateral actions and not sensory attention. Nature 313: 679–682

Carlsson M, Carlsson A (1989) The NMDA antagonist MK-801 causes marked locomotor stimulation in monoamine depleted mice. J Neural Transm 75: 221–226

Carlsson M, Carlsson A (1990) Interactions between glutamatergic and monoaminergic systems within the basal ganglia – implications for schizophrenia and Parkinson's disease. Trends Neurosci 13: 272–276

Carter CJ (1982) Topographical distribution of possible glutamatergic pathways from the frontal cortex to the striatum and substantia nigra in rats. Neuropharmacology 21: 379–383

Castaneda E, Whishaw IQ, Robinson TE (1990) Changes in striatal dopamine neurotransmission assessed with microdialysis following recovery from a bilateral 6-OHDA lesion: variation as a function of lesion size. J Neurosci 10: 1847–1854

Ceci A, French ED (1989) Phencyclidine-induced activation of ventral tegmental A10 dopamine neurons is differentially affected by lesions of the nucleus accumbens and medial prefrontal cortex. Life Sci 45: 637–646

Chapman AG, Swan JH, Patel S, Graham JL, Meldrum BS (1990) Cerebroprotective and anticonvulsant action of competitive and non-competitive NMDA antagonists. In: Lubec G, Rosenthal GA (eds) Amino acids: chemistry, biology and medicine. ESCOM, Leiden, pp 219–232

Clineschmidt BV, Martin GE, Bunting PR, Papp NL (1982) Central sympathomimetic activity of (+)-S-methyl-10,11-dihydro-SH-dibenzo[a,d]cyclohepten-5,10-imine (MK-801), a substance with potent anticonvulsant, central sympathomimetic, and apparent anxiolytic properties. Drug Dev Res 2: 135–145

Clow DW, Lee SJ, Hammer Jr RP (1991) Competitive (AP S) and non-competitive (MK-801) NMDA receptor antagonists differentially alter glucose utilization in rat cortex. Synapse 7: 260–268

Colpaert FC (1987) Pharmacological characteristics of tremor, rigidity and hypokinesia induced by reserpine in rat. Neuropharmacology 26: 1431–1440

Cools AR (1986) Mesolimbic dopamine and its control of locomotor activity in rats: differences in pharmacology and light/dark periodicity between the olfactory tubercle and the nucleus accumbens. Psychopharmacology 88: 451–459

Costall B, Domeney AM, Kelly ME, Naylor RJ (1991) Pharmacological models in the development of antipsychotic drugs – new strategies. In: Olivier B, Mos J, Slangen JL (eds) Animals models psychopharmacology. Birkhauser, Basel, pp 253–263

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

Deutch AY, Tam SY, Freeman AS, Bowers Jr MB, Roth RH (1987) Mesolimbic and mesocortical dopamine activation induced by phencyclidine: contrasting pattern to striatal response. Eur J Pharmacol 134: 257–264

DiChiara G (1990) In-vivo brain dialysis of neurotransmitters. Trends Pharmacol Sci 11: 116–121

Divac I, Öberg G (1979) The neostriatum. Pergamon Press, Oxford, pp 291–313

Elliott PJ, Close SP, Walsh DM, Hayes AG, Marriott AS (1990) Neuroleptic-induced catalepsy as a model of Parkinson's disease. J Neural Transm [PD-Sect] 2: 79–89

Ferré S, Rubio A, Fuxe K (1991) Stimulation of adenosine A_2 receptors induces catalepsy. Neurosci Lett 130: 162–164

Fibiger HC, Zis AP, Philips AG (1975) Haloperidol-induced disruption of conditioned avoidance: attenuation by prior training or by cholinergic drugs. J Pharmacol 30: 309–314

Fonnum F (1984) Glutamate: a neurotransmitter in mammalian brain. J Neurochem 42: 1–11

Fowler SC, Ford KE, Gramling SE, Nail GL (1984) Acute and subchronic effects of neuroleptics on quantitative measures of discriminative motor control in rats. Psychopharmacology 84: 369–373

Fowler SC, LaCerra MM, Ettenberg A (1986) Effects of haloperidol on the biophysical characteristics of operant responding: implications for motor and reinforced processes. Pharmacol Biochem Behav 25: 791–796

Fray PJ, Sahakian BJ, Robbins TW, Koob GF, Iversen SD (1980) An observational method for quantifying the behavioural effects of dopamine agonists: contrasting effects of d-amphetamine and apomorphine. Psychopharmacology 69: 253–259

French ED, Ceci A (1990) Non-competitive N-methyl-D-aspartate antagonists are potent activators of ventral tegmental A10 dopamine neurons. Neurosci Lett 119: 159–162

French ED, Ferkany J, Abreu M, Levenson S (1991) Effects of competitive N-methyl-D-aspartate antagonists on midbrain dopamine neurons: an electrophysiological and behavioural comparison to phencyclidine. Neuropharmacology 30: 1039–1046

Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Monsma Jr FJ, Sibley DR (1990) D_1 and D_2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science 250: 1429–1432

Girault J-A, Halpain S, Greengard P (1990) Excitatory amino acid antagonists and Parkinson's disease. Trends Neurosci 13: 325–326

Goodwin P, Starr BS, Starr MS (1992) Motor responses to dopamine D1 and D2 agonists in the reserpine-treated mouse are affected differentially by the NMDA receptor antagonist MK 801. J Neural Transm [PD-Sect] 4: 15–26

Greenamyre JT, Young AB (1989) Synaptic localization of striatal NMDA, quisqualate and kainate receptors. Neurosci Lett 101: 133–137

Greenamyre JT, O'Brien CF (1991) N-methyl-D-aspartate antagonists in the treatment of Parkinson's disease. Arch Neurol 48: 977–981

Greenamyre JT, Zhang ZM, Gash DM, Kurlan RK, Turski L (1991) A glutamate antagonist, NBQX, has antiparkinsonian effects in MPTP-treated monkeys. Neurology [Abstr] 41: 1163

Haber SN, Groenewegen HJ, Grove EA, Nauta WJH (1985) Efferent connections of the ventral pallidum: evidence of a dual striato pallidofugal pathway. J Comp Neurol 235: 322–235

Hauber W (1990a) The dopamine-glutamate interaction as a target of parkinsonian therapy. Naunyn-Schmiedebergs Arch Pharmacol [Suppl] 342: 12

Hauber W (1990b) A novel reaction time task for investigating force and time parameters in rats. Experientia 46: 1084–1088

Hauber W (1992) Anti-akinetic and anti-bradykinetic effects of NMDA antagonists in a rodent model of Parkinson's disease. In: Elsner N, Richter D (eds) Rhythmogenesis in neurons and networks. Thieme, Stuttgart New York, p 593

Hauber W, Schmidt WJ (1989) Effects of intrastriatal blockade of glutamatergic transmission on the acquisition of T-maze and radial maze tasks. J Neural Transm 78: 29–41

Hauber W, Schmidt WJ (1990) The NMDA antagonist dizocilpine reverses haloperidol-induced movement initiation deficits. Behav Brain Res 41: 161–166

Hauber W, Bubser M, Schmidt WJ (1991) Cortico-striatal functional loops and reaction time performance in rats. Eur J Neurosci [Suppl] 4: 167

Heal DJ, Frankland ATJ, Buckett WR (1990) A new and highly sensitive method for measuring 3-methoxytyramine using HPLC with electrochemical detection. Studies with drugs which alter dopamine metabolism in the brain. Neuropharmacology 29: 1141–1150

Hillegaart V, Ahlenius S (1987) Effect of raclopride on exploratory locomotion activity, treadmill locomotion, conditioned avoidance behaviour and catalepsy in rats: behavioural profile comparisons between raclopride, haloperidol and preclamol. Pharmacol Toxicol 60: 350–354

Holemans S, Javoy F, Agid Y, Laterre EC, Maloteaux J-M (1991) [^{3}H]MK-801 binding to NMDA glutamatergic receptors in Parkinson's disease and progressive supranuclear palsy. Brain Res 565: 154–157

Imperato A, Scrocco MG, Bacchi S, Angelucci L (1990a) NMDA receptors and in vivo dopamine release in the nucleus accumbens and caudatus. Eur J Pharmacol 187: 555–556

Imperato A, Honoré T, Jensen LH (1990b) Dopamine release in the nucleus caudatus and in the nucleus accumbens is under glutamatergic control through non-NMDA receptors: a study in freely-moving rats. Brain Res 530: 223–228

Irifune M, Shimizu T, Nomoto M (1991) Ketamine-induced hyperlocomotion associated with alteration of presynaptic components of dopamine neurons in the nucleus accumbens of mice. Pharmacol Biochem Behav 40: 399–407

Jellinger KA (1991) Pathology of Parkinson's disease. Changes other than the nigrostriatal pathway. Mol Chem Neuropathol 14: 153–197

Jonsson G (1983) Chemical lesioning technique: monoamine neurotoxins. In: Björklund A, Hökfelt T (eds) Handbook of chemical neuroanatomy, vol 1. Methods in chemical neuroanatomy. Elsevier, Amsterdam, pp 463–507

Kannari K, Markstein R (1991) Dopamine agonists potentiate antiakinetic effects of competitive NMDA-antagonists in monoamine-depleted mice. J Neural Transm 84: 211–220

Kelly PH, Seviour PW, Iversen SD (1975) Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Res 94: 507–522

Keseberg U, Bubser M, Schmidt WJ (1991) Effects of the non-competitive NMDA antagonist dizocilpine on open-field activity and on dopamine metabolism in the rat. In: Elsner N, Penzlin H (eds) Synapse, transmission, modulation. Proceedings 19th Göttingen Neurobiol Conf, Göttingen. Thieme, Stuttgart, p 448

Klockgether T, Turski L (1990) NMDA antagonists potentiate antiparkinsonian actions of L-DOPA in monoamine-depleted rats. Ann Neurol 28: 539–546

Klockgether T, Turski L, Honoré T, Zhang Z, Gash DM, Kurlan R, Greenamyre JT (1991) The AMPA receptor antagonist NBQX has antiparkinsonian effects in monoamine-depleted rats and MPTP-treated monkeys. Ann Neurol 30: 717–723

Kornhuber J, Kim J, Kornhuber ME, Kornhuber HH (1984) The corticonigral projection: Reduced glutamate content in the substantia nigra following frontal cortex ablation in the rat. Brain Res 322: 124–126

Kornhuber J, Bormann J, Retz W, Hübers M, Riederer P (1989) Memantine displaces [^{3}H]MK-801 at therapeutic concentrations in postmortem human frontal cortex. Eur J Pharmacol 166: 589–590

Kretschmer BD, Schmidt WJ (1992) The anticataleptic potential of an antagonist at the strychnine-insensitive glycine receptor. In: Elsner N, Richter DW (eds) Rhythmogenesis in neurons and networks. Proceedings of the 20th Göttingen Neurobiology Conference. G Thieme, Stuttgart New York, pp 595

Kretschmer BD, Zadow B, Volz TL, Volz L, Schmidt WJ (1992) The contribution of the different binding sites of the N-methyl-D-aspartate (NMDA) receptor to the expression of behavior. J Neural Transm 87: 23– 35

Liljequist S, Ossowska K, Grabowska-Andén M, Andén NE (1991) Effect of the NMDA receptor antagonist, MK-801, on locomotor activity and on the metabolism of dopamine in various brain areas of mice. Eur J Pharmacol 195: 55–61

Ljungberg T, Ungerstedt U (1978) Classification of neuroleptic drugs according to their ability to inhibit apomorphine-induced locomotion and gnawing: evidence for two different mechanisms of action. Psychopharmacology 56: 239–247

Ljungberg T, Ungerstedt U (1985) A rapid and simple behavioural screening method for simultaneous assessment of limbic and striatal blocking effects of neuroleptic drugs. Pharmacol Biochem Behav 23: 479–485

Löschmann P-A, Lange KW, Kunow M, Rettig K-J, Jähnig P, Honoré T, Turski L, Wachtel H, Jenner P, Marsden CD (1991) Synergism of the AMPA-antagonist NBQX and the NMDA-antagonist CPP with L-Dopa in models of Parkinson's disease. J Neural Transm [PD-Sect] 3: 203–213

Lowe DA, Neijt HC, Aebischer B (1990) D-CPP-ene (SDZ EAA 494), a potent and competitive N-methyl-D-aspartate (NMDA) antagonist: effect on spontaneous activity and NMDA-induced depolarizations in the rat neocortical slice preparation, compared with other CPP derivatives and MK-801. Neurosci Lett 113: 315–321

Lyon M, Robbins T (1975) The action of central nervous system stimulant drugs: a general theory concerning amphetamine effects. Curr Dev Psychopharmacol 2: 79–163

Maj J, Sowinska H, Baran L, Sarnek J (1974) Pharmacological effects of 1,3-dimethyl-5-aminoadamantane, a new adamantane derivative. Eur J Pharmacol 26: 9–14

Mehta AK, Ticku MK (1990) Role of N-methyl-D-aspartate (NMDA) receptors in experimental catalepsy in rats. Life Sci 46: 37–42

Monaghan DT, Cotman CW (1985) Distribution of N-methyl-D-aspartate-sensitive L-[^{3}H]glutamate-binding sites in rat brain. J Neurosci 5: 2909-2919

Montgomery EB, Buchholz SR (1991) The striatum and motor cortex in motor initiation and execution. Brain Res 549: 222–229

Montgomery EB, Nuessen J, Gorman DS (1991a) Reaction time and movement velocity abnormalities in Parkinson's disease under different task conditions. Neurology 41: 1476–1481

Montgomery EB, Gorman DS, Nuessen J (1991b) Motor initiation versus execution in normal and Parkinson's disease subjects. Neurology 41: 1469–1475

Morelli M, DiChiara G (1990) MK-801 potentiates dopaminergic D_1 but reduces D_2 responses in the 6-hydroxydopamine model of Parkinson's disease. Eur J Pharmacol 182: 611–612

Nieoullon A, Chermay A, Glowinski J (1978) Release of dopamine under punctate electrical stimulations of the motor and associative visual areas of the cerebral cortex, in both caudate nucleus and in the substantia nigra in the cat. Brain Res 145: 69–83

Ögren SO, Fuxe K (1988) D_1- and D_2-receptor antagonists induce catalepsy via different efferent striatal pathways. Neurosci Lett 85: 333–338

Ottersen OP, Storm-Mathisen J (1986) Neurons containing or accumulating transmitter amino acids. In: Björklund A, Hökfeldt T, Kuhar MK (eds) Handbook of chemical neuroanatomy, vol 3. Classical transmitter and transmitter receptors in the CNS. Elsevier Science, Amsterdam, pp 141–246

Randrup A, Munkvad I (1967) Stereotyped behaviour produced by amphetamine in several animal species and man. Psychopharmacologia 11: 300–310

Rao TS, Kim HS, Lehmann J, Martin LL, Wood PL (1990a) Interactions of phencyclidine receptor agonist MK-801 with dopaminergic system: regional studies in the rat. J Neurochem 54: 1157–1162

Rao TS, Kim HS, Lehmann J, Martin LL, Wood PL (1990b) Selective activation of dopaminergic pathways in the mesocortex by compounds that act at the phencyclidine (PCP) binding site: tentative evidence for PCP recognition sites not coupled to N-methyl-D-aspartate (NMDA) receptors. Neuropharmacology 29: 225–230

Rao TS, Cler JA, Mick SJ, Emmett MR, Farah Jr JM, Contreras PC, Iyengar S, Wood PL (1991) Neurochemical interactions of competitive N-methyl-D-aspartate antagonists with dopaminergic neurotransmission and the cerebellar cyclic GMP system: functional evidence for a phasic glutamatergic control of the nigrostriatal dopaminergic pathway. J Neurochem 56: 907–913

Reid MS, Herrera-Marschitz M, Hökfelt T, Lindefors N, Persson H, Ungerstedt U (1990) Striatonigral GABA, dynorphin, substance P, and neurokinin A modulation of nigrostriatal dopamine release: evidence for direct regulatory mechanisms. Exp Brain Res 82: 293–303

Robertson A, MacDonald C (1984) Atypical neuroleptics clozapine and thioridazine enhance amphetamine-induced stereotypy. Pharmacol Biochem Behav 21: 97–101

Robertson RG, Clarke CE, Boyde S, Sambrook MA, Crossman AR (1990a) The role of striatopallidal neurones utilising gamma amino butyric acid in the pathophysiology of MPTP-induced parkinsonism in the primate; evidence from (^{3}H) flunitrazepam autoradiography. Brain Res 531: 95–104

Robertson RG, Graham WC, Sambrook MA, Crossman AR (1990b) Extracellular levels of amino acids in the basal ganglia of the conscious primate before and after MPTP studied by intracerebral microdialysis. Neurosci Lett [Suppl] 38: 13

Robinson TE, Whishaw IQ (1988) Normalization of extracellular dopamine in striatum following recovery from a partial unilateral 6-OHDA lesion of the substantia nigra: a microdialysis study in freely moving rats. Brain Res 450: 209–224

Robinson TE, Castaneda E, Whishaw IQ (1990) Compensatory changes in striatal dopamine neurons following recovery from injury induced by 6-OHDA or methamphetamine: a review of evidence from microdialysis studies. Can J Psychol 44: 253–275

Rose S, Nomoto M, Kelly E, Kilpatrick G, Jenner P, Marsden CD (1989) Increased caudate dopamine turnover may contribute to the recovery of motor function in marmosets treated with the dopaminergic neurotoxin MPTP. Neurosci Lett 101: 305–310

Russ H, Mihatsch W, Gerlach M, Riederer P, Przuntek H (1991) Neurochemical and behavioural features induced by chronic low dose treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in the common marmoset: implications for Parkinson's disease? Neurosci Lett 123: 115– 118

Sanberg PR (1980) Haloperidol-induced catalepsy is mediated by postsynaptic dopamine receptors. Nature 284: 472–473

Sanberg PR, Bunsey MD, Giordano M, Norman AB (1988) The catalepsy test: its ups and downs. Behav Neurosci 102: 748–759

Santiago M, Rollema H, de Vries JB, Westerink BHC (1991) Acute effects of intranigral application of MPP^+ on nigral and bilateral striatal release of dopamine simultaneously recorded by microdialysis. Brain Res 538: 226– 230

Sayre LM (1989) Biochemical mechanisms of action of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Toxicol Lett 48: 121–149

Scatton B, Worms P, Lloyd KG, Bartholini G (1982) Cortical modulation of striatal function. Brain Res 232: 331–343

Schallert T, Teitelbaum P (1981) Haloperidol, catalepsy, and equilibrating functions in the rat: a antagonistic interaction of clinging and labyrinthine righting reactions. Physiol Behav 27: 1077–1083

Schmidt WJ (1984) L-dopa and apomorphine disrupt long-but not short-behavioural chains. Physiol Behav 33: 671–680

Schmidt WJ (1986a) Intrastriatal injection of DL-2-amino-5-phosphonovaleric acid (AP-S) induces sniffing stereotypy that is antagonized by haloperidol and clozapine. Psychopharmacology 90: 123–130

Schmidt WJ (1986b) Striatal glutamic acid and the behaviour of rats. Verh Dtsch Zool Ges 79: 416–417

Schmidt WJ, Bury D (1988) Behavioural effects of N-methyl-D-aspartate in the anterodorsal striatum of the rat. Life Sci 43: 545–549

Schmidt WJ, Bischoff C (1988) Dopaminergic behavioural responses modulated by NMDA receptor antagonists. Psychopharmacology 96: 196

Schmidt WJ, Bubser M (1989) Anticataleptic effects of the N-methyl-D-aspartate antagonist MK-801 in rats. Pharmacol Biochem Behav 32: 621–623

Schmidt WJ, Bubser M, Hauber W (1990a) Excitatory amino acids and Parkinson's disease. Trends Neurosci 13: 46

Schmidt WJ, Bubser M, Hauber W (1990b) Anticataleptic effects of NMDA receptor antagonists. Eur J Neurosci [Suppl] 3: 118

Schmidt WJ, Zadow B, Kretschmer BD, Hauber W (1991) Anticataleptic potencies of glutamate-antagonists. Amino Acids 1: 225–237

Schultz W (1982) Depletion of dopamine in the striatum as an experimental model of parkinsonism: direct effects and adaptive mechanisms. Progr Neurobiol 18: 121–166

Schultz W, Studer A, Romo R, Sundström E, Jonsson G, Scarnati E (1989) Deficits in reaction times and movement times as correlates of hypokinesia in monkeys with MPTP-induced striatal dopamine depletion. J Neurophysiol 61: 651–668

Schuster G (1990) AP-S injected into the medial substantia nigra pars reticulata induces stereotyped behavior. In: Elsner N, Roth G (eds) Brain – perception cognition. Proceedings 18th Göttingen Neurobiol Conf. G Thieme, Stuttgart New York, p 499

Schuster G, Schmidt WJ (1988) Glutamatergic control of behaviour in the midbrain of rats: effects of the NMDA-antagonist AP-5. In: Elsner N, Barth F (eds) Interfaces between environment and behaviour. Proceedings 16th Göttingen Neurobiol Conf. G Thieme, Stuttgart New York, p 359

Shimizu N, Duan S, Hori T, Oomura Y (1990) Glutamate modulates dopamine release in the striatum as measured by brain microdialysis. Brain Res Bull 25: 99–102

Skjoldager P, Fowler SC (1988) Effects of pimozide, across doses and within sessions on discriminated lever release performance in rats. Psychopharmacology 96: 21–28

Spirduso WW, Abraham LD, Wolf MD (1981) Effects of chlorpromazine on escape and avoidance responses: a closer look. Pharmacol Biochem Behav 14: 433–438

Spirduso WW, Gilliam PE, Schallert T, Upchurch M, Vaughn DM, Wilcox RE (1985) Reactive capacity: a sensitive behavioral marker of movement initiation and nigrostriatal dopamine function. Brain Res 335: 45–54

Stelmach GE, Worringham CJ (1988) The preparation and production of isometric force in Parkinson's disease. Neuropsychologia 26: 93–103

Svensson A, Pileblad E, Carlsson M (1991) A comparison between the non-competitive NMDA antagonist dizocilpine (MK-801) and the competitive NMDA antagonist D-CPPene with regard to dopamine turnover and locomotor-stimulatory properties in mice. J Neural Transm 85: 117–129

Tamminga CA, Kaneda H, Buchanan R, Kirkpatrick B, Thaker GK, Yablonski MB, Holcomb HH (1991) The limbic system in schizophrenia. Pharmacologic and metabolic evidence. In: Tamminga CA, Schulz SC (eds) Advances in neuropsychiatry and psychopharmacology, vol 1. Schizophrenia research. Raven Press, New York, pp 99–109

Tanii Y, Nishikawa T, Umino A, Takahashi K (1990) Phencyclidine increases extracellular dopamine metabolites in rat medial frontal cortex as measured by in vivo dialysis. Neurosci Lett 112: 318–323

Tiedtke PI, Bischoff C, Schmidt WJ (1990) MK-801-induced stereotypy and its antagonism by neuroleptic drugs. J Neural Transm 81: 173–182

Ungerstedt U (1974) Brain dopamine neurons and behavior. In: Schmitt FO, Worden FG (eds) The neurosciences: third study program. Cambridge Mass, London, pp 695–703

Wachtel H (1991) Antiparkinsonian dopamine agonists: a review of the pharmacokinetics and neuropharmacology in animal and humans. J Neural Transm 3: 151–201

Walaas I (1981) Biochemical evidence for overlapping neocortical and allocortical glutamate projections to the nucleus accumbens and rostral caudatoputamen in the rat brain. Neuroscience 6: 399–405

Watkins JC (1988) Thirty years of excitatory amino acid research. In: Cavalheiro EA, Lehman J, Turski L (eds) Neurology and neurobiology. Frontiers in excitatory amino acid research. New York, pp 3–10

Wegener S, Schmidt WJ, Ehret G (1988) Haloperidol- and apomorphine-induced changes in pup searching behaviour of house mice. Psychopharmacology 95: 271–275

Westerink BHC (1985) Sequence and significance of dopamine metabolism in the rat brain. Neurochem Int 7: 221–227

Wierzbicka MM, Wiegner AW, Logigian EL, Young RR (1991) Abnormal most-rapid isometric contractions in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 54: 210–216

Wong EHF, Knight AR, Ransom R (1987) Glycine modulates [3H]MK-801 bing to the NMDA receptor in rat brain. Eur J Pharmacol 142: 487–488

Wood PL, Altar CA (1988) Dopamine release in vivo from nigrostriatal, mesolimbic, and mesocortical neurons: utility of 3-methoxytyramine measurements. Pharmacol Rev 40: 163–187

Worms P, Willigens M-T, Continsouza-Blanc D, Lloyd KG (1985) The effect of different types of cortical lesions on drug-induced catalepsy in rat pharmacological analysis. Eur J Pharmacol 113: 53–59

Yoshida Y, Ono T, Kizu A, Fukushima R, Miyagishi T (1991) Striatal N-methyl-D-asparate receptors in haloperidol-induced catalepsy. Eur J Pharmacol 203: 173–180

Young AB, Dauth GW, Hollingsworth Z, Penney JB, Kaatz K, Gilman S (1990) Quisqualate- and NMDA-sensitive [^{3}H]glutamate binding in primate brain. J Neurosci Res 27: 512–521

Zadow B, Schmidt WJ (1992a) The effects of the selective AMPA-antagonist NBQX in an animal model of Parkinson's disease. In: Elsner N, Richter DW (eds) Rhythmogenesis in neurons and networks. Proceedings of the 20th Göttingen Neurobiology Conference. G Thieme, Stuttgart New York, pp 596

Zadow B, Schmidt WJ (1992b) EP-lesion potentiates the anticataleptic effects of glutamate antagonists. J Psychopharm BAP/EBPS Abstract Book A 65

Zigmond MJ, Berger TW, Grace AA, Stricker EM (1989) Compensatory responses to nigrostriatal bundle injury. Studies with 6-hydroxydopamine in an animal model of parkinsonism. Mol Chem Neuropathol 10: 185–200

Zigmond MJ, Abercrombie ED, Berger TW, Grace AA, Stricker EM (1990) Compensations after lesions of central dopaminergic neurons: some clinical and basal implications. Trends Neurosci 13: 290–296

Authors' address: Dr. W. J. Schmidt, University of Tübingen, Neuropharmacology Division, Mohlstrasse 54/1, D-W-7400 Tübingen, Federal Republic of Germany

Abbreviations and drugs

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate
AP-5	2-amino-5-phosphonovaleric acid
AP-7	2-amino-7-phosphonoheptanoic acid
CGP 37849	(e)-2-amino-4-methyl-5-phosphono-3-pentanoic acid
CGP 39551	(e)-2-amino-4-methyl-5-phosphono-3-pentanoic acid ethylester
CGS-19755	cis-4-phosphonomethyl-2-piperidine-carboxylic acid
CPP	3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid
CPPene	see SDZ EAA 494
DA	dopamine
DCS	D-cycloserine
Dizocilpine (MK-801)	(+)-S-methyl-10,11-dihydro-SH-dibenz[a,d]-cyclohepten-5,10-imine
L-DOPA	L-3,4,-dihydroxyphenylalanine
DOPAC	dihydroxyphenylacetic acid
GABA	gamma-aminobutyric acid
GLU	L-glutamic acid
GPe	globus pallidus external segment
GPi	globus pallidus internal segment
GYKI 52466	(4-amino-phenyl)-4-methyl-7,8-methylene-dioxy-SH-2,3-benzodiazepine-HCl
HVA	homovanillic acid
α-MPT	α-methyl-p-tyrosine
MPP+	1-methyl-4-phenylpyridinium
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
3-MT	3-methoxytyramine
NBQX	6-nitro-7-sulfamobenzo(f)quinoxaline-2,3-dione
NMDA	N-methyl-d-aspartate
NPC 12626	2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid hydrate
6-OHDA	6-hydroxydopamine
SCH 23390	(R)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepin-7-ol
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
SDZ EAA 494 (CPPene)	(E)-4-(3-phosphonoprop-2-enyl)-piperazine-2-carboxylic acid
STN	subthalamic nucleus
THAL	thalamus