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Effects of the antiparkinsonian drug budipine on central neurotransmitter systems

Thomas Klockgether [a,*], Ullrich Wüllner [a], Joachim Peter Steinbach [a], Vibke Petersen [b], Lechoslaw Turski [c], Peter-Andreas Löschmann [a]

[a] *Department of Neurology, University of Tübingen, Hoppe-Seyler-Straße 3, D-72076 Tübingen, Germany*
[b] *Novo Nordisk A / S, CNS Division, Måløv, Denmark*
[c] *Research Laboratories, Schering AG, Müllerstraße 178, D-13042 Berlin, Germany*

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Abstract

Budipine is a novel antiparkinsonian drug which is particularly beneficial in the treatment of parkinsonian tremor. The mechanism of action of budipine is not fully understood. To study whether budipine has dopaminergic activity in vivo, we used the 6-hydroxydopamine rotational model of Parkinson's disease. Budipine (0.78–12.5 mg/kg i.p.) did not induce ipsilateral or contralateral rotations, suggesting that it does not possess direct or indirect dopaminergic activity. This conclusion is further supported by the observation that budipine (10 mg/kg) i.v. did not facilitate striatal dopamine release measured in vivo by brain microdialysis. To investigatate possible antimuscarinic and *N*-methyl-D-aspartic acid (NMDA) antagonistic properties of budipine, we compared budipine with the antimuscarinic antiparkinsonian drug biperiden and the NMDA receptor antagonist 3-[(±)-2-carboxypiperazine-4-yl]-propyl-1-phosphonic acid (CPP). In receptor-binding assays, budipine inhibited thienylcyclohexylpiperidyl-3,4-[^{3}H](n) ([^{3}H]TCP) (2.5 nM)-binding with an IC_{50} of 36 μM and [^{3}H]3-quinuclidinol benzilate-binding with an IC_{50} of 1.1 μM. The respective values for biperiden were 170 and 0.053 μM. In line with these findings, budipine and CPP increased the threshold for NMDA-induced seizures in mice with an ED_{50} of 10.2 and 4.4 mg/kg, respectively, whereas biperiden was not effective. In 6-hydroxydopamine-lesioned rats, budipine (3.13–12.5 mg/kg) and CPP (0.1–0.39 mg/kg) increased the number of contralateral rotations induced by apomorphine, whereas biperiden was not effective. The present data suggest that budipine acts by blocking muscarinic and NMDA transmission while facilitation of dopaminergic transmission does not appear to contribute to its in vivo action. In comparison to biperiden, which has also antimuscarinic and NMDA receptor antagonistic properties, the anti-NMDA action of budipine is more prominent.

Keywords: Biperiden; Budipine; Muscarinic; NMDA (*N*-methyl-D-asparate); Parkinsonism

1. Introduction

Budipine (1-*t*-butyl-4,4-diphenylpiperidine) (Byk-Gulden, Konstanz, Germany) is a novel antiparkinsonian agent which is currently being studied in phase III clinical trials in Europe. Additional therapy with budipine significantly improved parkinsonian symptoms in a double-blind placebo-controlled study in 31 patients with Parkinson's disease (Jellinger and Bliesath, 1987). In 60 patients with Parkinson's disease, budipine was more effective than amantadine (Iizuka and Fischer, 1986). Clinical experience shows that budipine is particularly effective for treatment of parkinsonian tremor (Jellinger and Bliesath, 1987; Spieker et al., 1995). Budipine has a plasma half-time of more than 30 h, which makes it suitable for the managment of patients with a fluctuating response to levodopa (Zech et al., 1985). In fact, evidence from an open-label study suggests that add-on therapy with budipine reduces the need for levodopa and improves daily oscillations in patients with advanced Parkinson's disease (Siegfried and Fischer, 1985). Another positive feature of budipine is its relatively low propensity to produce side-effects.

The mechanism of action of budipine has not yet been fully elucidated. Initial observations that budipine reverses the cataleptic state induced by neuroleptics suggested that it might act upon the dopaminergic system (Menge and Brand, 1982). Receptor-binding studies, however, failed to demonstrate specific binding of budipine to dopamine receptors (Przuntek and Stasch, 1985). Furthermore, budip-

* Corresponding author. Tel.: (49) (7071) 292141; fax: (49) (7071) 296507.

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ine does not affect KCl-induced release of dopamine and inhibits electrically induced dopamine release in brain slice preparations (Offermeier and Van Rooyen, 1985; Jackisch et al., 1993). Although budipine is a reversible inhibitor of the dopamine metabolizing enzyme monoamine oxidase B in vitro, in vivo the activity of monoamine oxidase B is not blocked by budipine (Menge and Brand, 1982). In contrast to these earlier studies, which failed to demonstrate consistent effects of budipine on the dopaminergic system, a recent in vitro study reported that budipine inhibits synaptosomal dopamine uptake and enhances spontaneous dopamine release from rabbit caudate nucleus slices (Jackisch et al., 1993).

A number of studies have found antimuscarinic properties of budipine. However, the affinity of budipine for cortical muscarinic receptors labeled by propylbenzilylcholine is ~20× lower than that of the antimuscarinic drug biperiden, which is widely used for the treatment of Parkinson's disease. Similarly, budipine inhibits the peripheral effects of acetylcholine in vitro but is by one or two orders of magnitude weaker than biperiden (Menge and Brand, 1985). We recently presented behavioral, electrophysiological and receptor-binding evidence that budipine is also a weak noncompetitive NMDA receptor antagonist with affinity for the phencyclidine-binding site within the NMDA receptor ionophore in the micromolar range (Klockgether et al., 1993). NMDA receptor antagonistic properties of budipine have been confirmed in subsequent studies (Jackisch et al., 1994; Porter and Greenamyre, 1995).

The present study was undertaken to further elucidate the mechanism of action of budipine. In particular, we wished to study whether budipine has effects on the dopaminergic system in vivo. To this end, we studied the action of budipine in the 6-hydroxydopamine rotational model of Parkinson's disease and measured striatal dopamine release by in vivo brain microdialysis. To characterize the antimuscarinic and anti-NMDA actions of budipine, we compared its action with that of biperiden and the NMDA receptor antagonist 3-[(±)-2-carboxypiperazine-4-yl]-propyl-1-phosphonic acid (CPP).

2. Materials and methods

2.1. Animals

Seizure experiments were performed in male NMRI mice (28–35 g; Interfauna, Tuttlingen, Germany). For microdialysis and rotational experiments, Wistar rats (400–590 g; Interfauna) were used. Animals were housed under standard conditions at a temperature of 22 ± 1°C and a 12-h light–dark cycle (light on from 06:00 to 18:00 h). They had free access to food and water. Experiments were performed between 09:00 and 17:00 h. All animal experiments were done in accordance with the animal protection guidelines and laws of the Federal Republic of Germany and had been approved by a regional committee on animal care.

2.2. Drug preparations

The following drugs were used: Budipine (Byk Gulden, Konstanz, Germany), biperiden (Sigma, St Louis, MO), 3-[(±)-2-carboxypiperazine-4-yl]-propyl-1-phosphonic acid (CPP; Tocris, Buckhurst Hill, UK), pargyline (Sigma), 6-hydroxydopamine (Sigma), apomorphine (Sandoz, Basle, Switzerland), amphetamine (Sigma), *N*-methyl-D-aspartic acid (NMDA; Tocris), kainic acid (Sigma) α-amino-3-hydroxy-5-tertbutyl-4-isoxazolepropionic acid (ATPA; Novo Nordisk, Måløv, Denmark). 6-Hydroxydopamine was dissolved in saline solution containing 0.02% ascorbic acid (Sigma). Apomorphine was dissolved in normal saline containing 10% (v/w) polyethoxylated castor oil (Cremophor EL; Fluka, Ulm, Germany). NMDA, kainic acid and ATPA were brought into solution with a minimum quantity of 1 N NaOH, and the final volume was made up with saline solution. The pH was adjusted to 7.4. All other drugs were dissolved in normal saline. All dosages refer to the free form (base, acid).

2.3. Rotational behavior in 6-hydroxydopamine-lesioned rats

For stereotaxic lesions of the substantia nigra, rats were pretreated with pargyline (25 mg/kg s.c.) and 30 min later 6-hydroxydopamine (16 μg/4 μl) was injected into the left substantia nigra under pentobarbital anesthesia (50 mg/kg i.p.). The stereotaxic coordinates were: AP −5.5, L 2.2, V −8.2 according to a stereotaxic atlas (Paxinos and Watson, 1982). After recovery of the animals from surgery and initial screening with apomorphine and amphetamine (see below), experiments started 2 months after the lesion. Animals were not used for longer than 6 months. Ipsiversive and contraversive rotations were registered by means of an automatic device consisting of 6 perspex bowls (40 cm diameter) and electro-mechanical transducer systems. The latter registered a count each time the animal moved through 36° in a clockwise or counterclockwise direction. In addition, full 360° rotations were registered for each direction. Animals were placed into the bowls and connected to the transducers following injection of test compounds. Counts and full circle rotations were accumulated in 10 min intervals. Only rotations were analysed since the number of rotation counts and full rotations show a robust correlation in animals exposed to apomorphine or amphetamine, respectively. Animals showing more than 30 contraversive rotations in 30 min when exposed to a standard dose of apomorphine (0.1 mg/kg s.c.) and more than 60 ipsiversive rotations in 60 min following treatment with amphetamine (1.56 mg/kg) at 1 and 2 weeks after the lesion were included in experi-

mental groups. Rats were allocated to treatment groups of 6–8 animals in a quasi-random fashion with the restriction that no animal received active or nonactive treatment more than twice consecutively. A wash-out period of 2 weeks was allowed between experiments.

2.4. In vivo brain microdialysis

A guide cannula provided with a dummy (CMA 12; Carnige Medicine, Stockholm, Sweden) was stereotaxically positioned into the left striatum under pentobarbital anesthesia (50 mg/kg i.p.). The stereotaxic coordinates were: AP 0.0, L 3.0, V −2.1 (Paxinos and Watson, 1982). Following surgery, the rats were individually housed for 3 days prior to the experiment. Microdialysis experiments were performed in freely moving animals. During the experiment, the dummy was replaced by the dialysis probe (outer diameter: 0.5 mm; type CMA 12; Carnige Medicine), which exceeded the tip of the guide cannula by 4 mm. The cannula was perfused using a syringe pump (Braun, Melsungen, Germany) with artificial cerebrospinal fluid (composition: NaCl 147 mM, KCl 5.3 mM, $CaCl_2$ 1.9 mM, $MgCl_2$ 1.1 mM, ascorbic acid 0.02 mM; pH 7.4). The flow rate was 0.75 μl/min. Samples were collected at 30-min intervals into vials located 5 cm distant from the outlet of the dialysis probe and were analysed immediately. At least 1 h following implantation 4 subsequent 30-min samples were used to determine basal catecholamine efflux. The effect of drugs was observed for 120 min. The location of the dialysis probes was verified in Cresyl violet-stained histological sections. Individual dialysis probes were tested for their recovery of monoamines by dialysis of standard solutions in vitro prior to use.

Analysis of biogenic amines and metabolites was performed using high-performance liquid chromatography with amperometric detection (electrochemical detector: Gynkotek M20, München, Germany; electrode: UniJet 6mm GC, Bioanalytical Systems, West Lafayette, IN; pump: Gynkotek M 480; injector: Rheodyne 3391, Cotati, CA) for simultaneous determination of dopamine, DOPAC (3,4-dihydroxyphenylacetic acid), HVA (homovanillic acid), and 3-methoxytyramine. The oxidation potential was set at 683 mV and readings were taken at 0.02 nA full scale. Separation of amines was performed on a C18 reversed-phase column (100 × 1 mm; StepStick, Bioanalytical Systems) in 5 μl samples. The mobile phase consisted of 100 mM sodium phosphate buffer, pH 3.1, containing 1 mM octansulfonic acid and 6% acetonitrile in deionized water. The flow was set at 70 μl/min. Quantification was performed on a 486 personal computer system using integration soft ware (Turbochrome 4; PE Nelson, Capetino, CA) and employing a three point external standard calibration curve. Raw amounts were corrected for probe recovery and are expressed as percentage of the efflux under baseline conditions.

2.5. Seizure test

Seizures were induced in mice by delivering the excitatory amino acids NMDA, kainic acid or ATPA into the lateral brain ventricle of unrestrained mice at a concentration of 1 nmol/μl and a constant rate of 5 μl/min. The threshold dose of NMDA, kainic acid or ATPA to produce seizures was determined by measuring the time until onset of seizures. Clonic movements of the limbs lasting more than 5 s were scored as a positive response. Drugs or vehicle was administered i.v. 30 min before seizure test, and the dose required to induce a 50% increase of the seizure threshold was determined (Steppuhn and Turski, 1993).

2.6. Receptor-binding experiments

Receptor-binding experiments were performed at 4°C with rat brain cortical membranes that had been extensively washed. NMDA receptors were studied with [^{3}H]CPP) (5 nM)-binding in 30 mM Tris–HCl buffer with 2.5 mM $CaCl_2$; the NMDA receptor ionophore was studied with thienylcyclohexylpiperidyl-3,4-[^{3}H](n) ([^{3}H]TCP) (2.5 nM)-binding in 5 mM Tris–HCl buffer; muscarinic receptors were studied with [^{3}H]3-quinuclidinol benzilate. The test values are given as IC_{50}, i.e. the concentration of the test substance which inhibits specific binding by 50% (Honoré et al., 1988).

2.7. Statistics

Statistical differences were calculated by ANOVA followed by a Tukey test.

3. Results

3.1. Rotational behavior in 6-hydroxydopamine-lesioned rats

Budipine (0.78–12.5 mg/kg i.p.), biperiden (0.39–6.25 mg/kg i.p.) and CPP (0.025–0.39 mg/kg i.p.) alone did not induce ipsilateral or contralateral rotations in rats bearing unilateral 6-hydroxydopamine lesions of the substantia nigra (Fig. 1). However, budipine (3.13–12.5 mg/kg i.p.) and CPP (0.1–0.39 mg/kg i.p.) increased the number of contralateral rotations induced by the mixed dopamine receptor agonist apomorphine (0.1 mg/kg i.p.). In contrast, biperiden had only a weak potentiating action on apomorphine-induced rotations that did not reach the level of statistical significance (Fig. 2).

3.2. In vivo brain microdialysis

Basal release of dopamine in the striatum of freely moving rats was 0.095 ± 0.03 pmol/30 min. The respec-

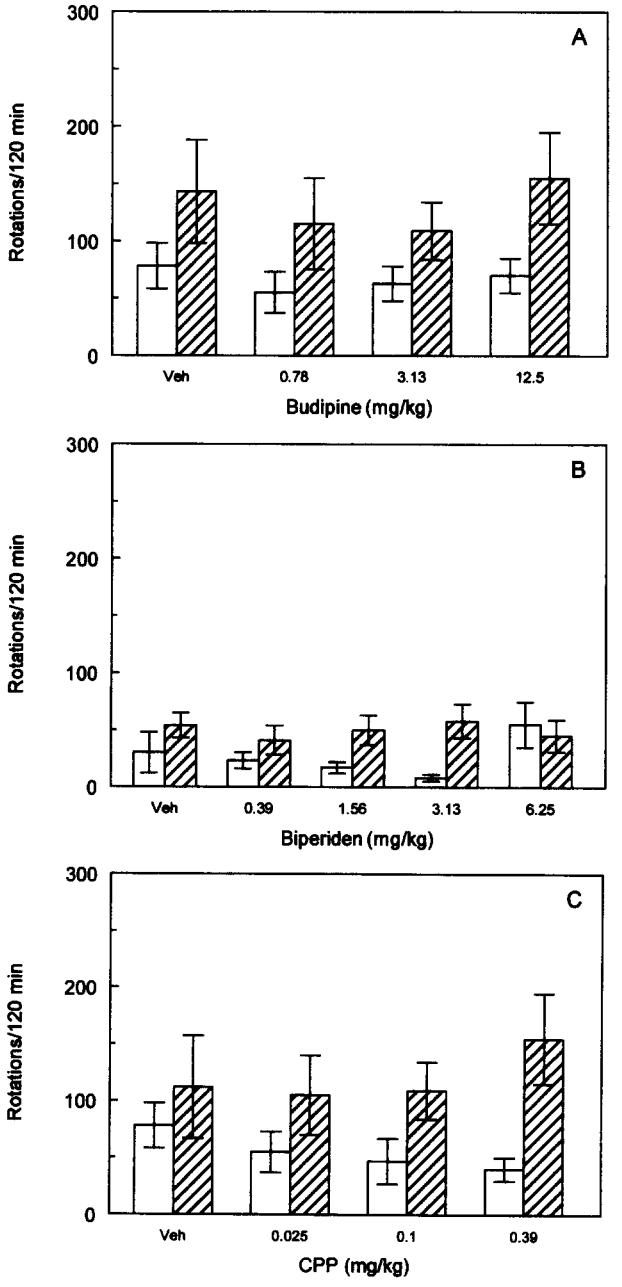

Fig. 1. Effect of (A) budipine (0.78–12.5 mg/kg i.p.), (B) biperiden (0.39–6.25 mg/kg i.p.) and (C) CPP (0.025–0.39 mg/kg i.p.) on the number of ipsilateral and contralateral rotations in unilaterally 6-hydroxydopamine-lesioned rats. Open bars represent ipsilateral rotations, hatched bars contralateral rotations. Experimental groups consisted of 6–8 animals. Data are presented as mean ± S.E.M. values. Statistical analysis was done by ANOVA.

tive values for dopamine metabolites were: DOPAC: 20.95 ± 5.24 pmol/30 min, HVA: 13.44 ± 3.44 pmol/30 min, 3-methoxytyramine: 0.22 ± 0.14 pmol/30 min. The release of dopamine and its metabolites DOPAC, HVA, and 3-methoxytyramine in the striatum was neither affected by vehicle (data not shown) nor by budipine (30 mg/kg i.p.) (Fig. 3).

3.3. Seizures

Budipine increased the threshold of NMDA-induced seizures with an ED_{50} of 10.2 mg/kg i.v. (95% confidence limits: 3.8–27.5 mg/kg, $n = 20$) without having an effect on seizures induced by kainic acid and ATPA. CPP antagonized NMDA-induced seizures with an ED_{50} of 4.4

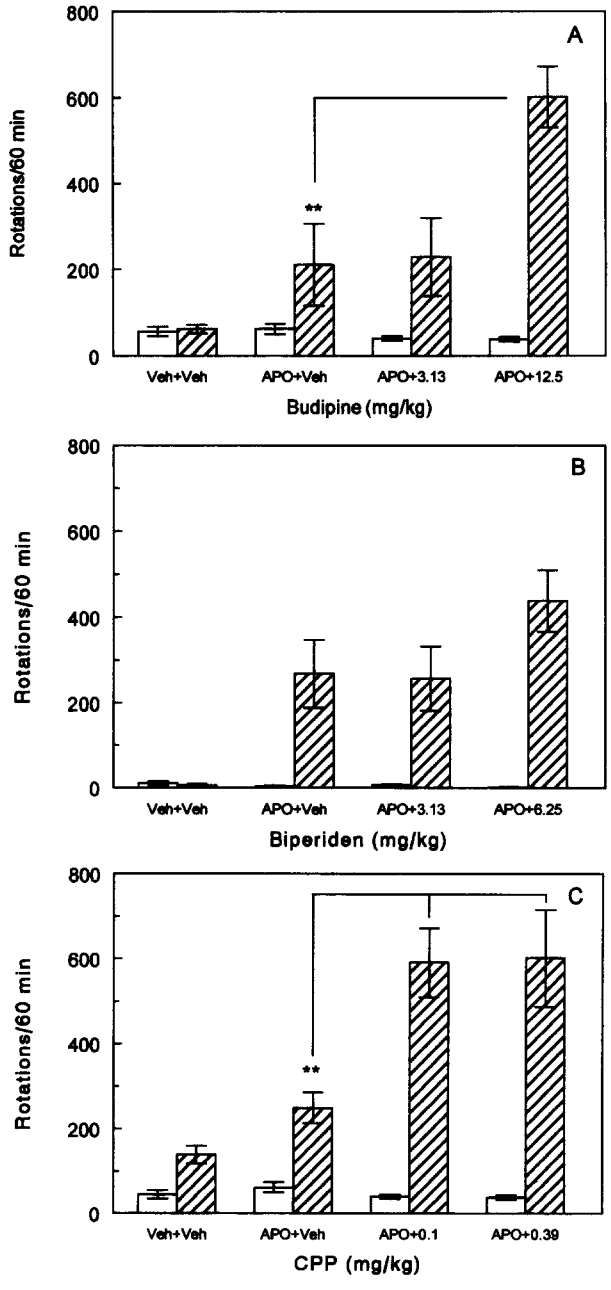

Fig. 2. Effect of (A) budipine (3.13–12.5 mg/kg i.p.), (B) biperiden (3.13–6.25 mg/kg i.p.) and (C) CPP (0.1–0.39 mg/kg i.p.) on the number of ipsilateral and contralateral rotations in unilaterally 6-hydroxydopamine-lesioned rats treated with apomorphine (APO; 0.1 mg/kg i.p.). Open bars represent ipsilateral rotations, hatched bars contralateral rotations. Experimental groups consisted of 6–8 animals. Data are presented as mean ± S.E.M. values. Statistical analysis was done by ANOVA. Significances: ** $P < 0.01$ vs. APO, Tukey test.

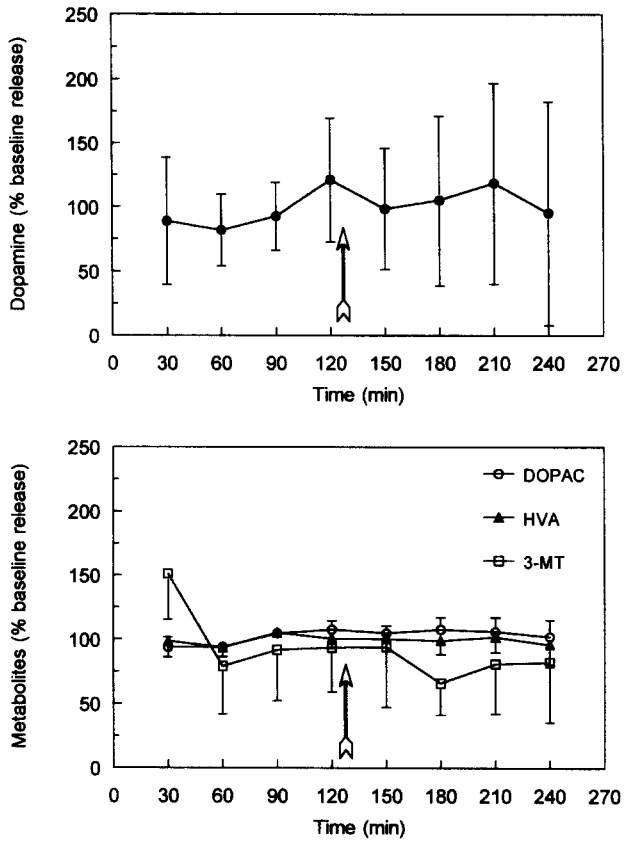

Fig. 3. Effect of budipine (30 mg/kg i.p.) on striatal release of dopamine (A) and its metabolites DOPAC, HVA and 3-methoxytyramine (B) as measured by in vivo brain microdialysis. The arrow indicates the time at which budipine was injected. Amounts of dopamine and its metabolites were corrected for probe recovery and are expressed as percentage of the efflux under baseline conditions. Data are presented as means ± S.E.M. values. The experimental group consisted of 6 animals. Statistical analysis was done by ANOVA.

mg/kg i.v., kainic acid-induced seizures with an ED_{50} of 25.5 mg/kg i.v. and ATPA-induced seizures with an ED_{50} of 23.6 mg/kg i.v. Neither biperiden nor vehicle had inhibiting effects on seizures induced by NMDA, kainic acid or ATPA (Table 1).

Table 1
Effects of budipine, biperiden and CPP on the threshold of seizures induced by continuous i.c.v. infusion of NMDA, kainic acid and ATPA in mice

	NMDA	Kainic acid	ATPA
Budipine	10.2 (3.8–27.5)	> 50	> 50
Biperiden	> 50	> 50	> 50
CPP	4.4 (3.0–6.5)	25.5 (16.4–39.5)	23.6 (17.8–31.3)

The data are given as the doses (mg/kg) of budipine, biperiden and CPP which led to a 50% increase of the seizure threshold after i.v. injection. The figures in the brackets represent the 95% confidence limits. Budipine, biperiden and CPP were administered i.v. Experimental groups consisted of 20–25 animals.

3.4. Receptor-binding studies

Budipine inhibited [^{3}H]TCP-binding with an IC_{50} of 36 μM and [^{3}H]3-quinuclidinol benzilate-binding with an IC_{50} of 1.1 μM. The respective values for biperiden were 170 μM ([^{3}H]TCP) and 0.053 ([^{3}H]3-quinuclidinol benzilate). Neither budipine nor biperiden had relevant affinity for the NMDA-binding site; the IC_{50} values for [^{3}H]CPP were 2200 and 1010 μM, respectively.

4. Discussion

Budipine is a novel antiparkinsonian drug which is particularly beneficial for the treatment of parkinsonian tremor. Previous studies have failed to identify a single mechanism of action of budipine. This study extends earlier findings and provides further evidence that budipine exerts its in vivo action by blocking glutamate and muscarinic receptors rather than by enhancing dopaminergic transmission.

Early observations that budipine reverses neuroleptic-induced catalepsy suggested that budipine might facilitate dopaminergic transmission (Menge and Brand, 1982). However, reversal of neuroleptic-induced catalepsy is not proof of a dopaminomimetic action because antimuscarinic drugs and competitive and noncompetitive NMDA receptor antagonists also antagonize catalepsy (Schmidt and Bubser, 1989). We have used the 6-hydroxydopamine rotational model of Parkinson's disease, which is highly sensitive for detection of dopaminomimetic drug actions in vivo. In this model, dopamine receptor agonists cause contralateral rotations by activating supersensitive postsynaptic dopamine receptors whereas compounds, such as amphetamine, that enhance the release of dopamine induce ipsilateral rotations. The failure of budipine to cause rotations in either direction strongly argues against direct or indirect dopaminomimetic actions of budipine. This conclusion is at variance with the recently reported finding that budipine at 10 μM inhibits synaptosomal dopamine uptake and enhances spontaneous dopamine release from rabbit caudate nucleus slices in vitro. However, budipine inhibits electrically evoked dopamine release in slice preparations (Jackisch et al., 1993). To study whether budipine releases dopamine in the striatum in vivo, we used in vivo brain microdialysis. We show that budipine did not affect extracellular concentrations of dopamine and its metabolites in the striatum. This observation in conjunction with the results of our behavioral experiments makes it unlikely that a dopamine-releasing action of budipine contributes significantly to the antiparkinsonian action of budipine in vivo.

Dopamine deficiency in the striatum of patients with Parkinson's disease leads to secondary changes in the activity of nondopaminergic transmitter systems lying

downstream to the dopaminergic nigrostriatal system. Traditional theories of the pathophysiology of Parkinson's disease emphasize the role of enhanced cholinergic activity in the striatum. The most compelling evidence for the importance of cholinergic mechanisms in Parkinson's disease is the antiparkinsonian action of antimuscarinic drugs, such as biperiden. Earlier studies have shown that budipine has weak antimuscarinic actions. Budipine inhibits acetylcholine-induced contractions of isolated guinea pig ileum in a dose-dependent way, yielding a pA_2 value of 6.68. The respective values for biperiden and atropine are 8.13 and 8.99 (Menge and Brand, 1982). Antimuscarinic actions of budipine are also evident in a number of in vivo paradigms, such as carbachol- and oxotremorine-induced salivation, acetylcholine-induced blood pressure decrease and drug-induced mydriasis. The efficacy of budipine in these paradigms, as judged from the ED_{50} values, is 40–150 × lower than that of biperiden and 100–1500 × lower than that of atropine (Menge and Brand, 1985). In slices of rabbit caudate nucleus, budipine facilitates electrically evoked acetylcholine release in the presence of acetylcholine esterase inhibitors, suggesting that it also possesses presynaptic antimuscarinic properties. The concentrations of budipine required for this effect are ~ 30 × higher than those of biperiden (Jackisch et al., 1993). The present binding data confirm that budipine possesses weak affinity for central muscarinic receptors. Budpine displaced [^{3}H]3-quinuclidinol benzilate from its binding sites with an IC_{50} of 1.1 μM while biperiden was active at a concentration which was 20 × lower.

Blockade of NMDA transmission by systemic administration of NMDA receptor antagonists potentiates the antiparkinsonian action of dopaminergic drugs in animal models of Parkinson's disease (Klockgether and Turski, 1990). Clinical experience with glutamate receptor antagonists in Parkinson's disease, however, is limited. In a placebo-controlled trial, the noncompetetive NMDA receptor antagonist memantine (Kornhuber et al., 1989), a compound that is licensed for the treatment of spasticity in Germany, improved the overall symptomatology of patients with Parkinson's disease with a preferential action on tremor (Schneider et al., 1984). In a recent open-label study performed with patients suffering from response fluctuations, memantine significantly reduced the daily time spent in off-periods (Rabey et al., 1992). Amantadine, which is widely used in the treatment of Parkinson's disease, might also act via blockade of NMDA receptors (Kornhuber et al., 1991). Milacemide, a glycine prodrug that is assumed to enhance NMDA transmission increases parkinsonian severity scores (Giuffra et al., 1993).

The suggestion that the NMDA receptor antagonistic properties of budipine might contribute to its antiparkinsonian action is supported by the following observations. (1) The action of budipine in the 6-hydroxydopamine rotational model of Parkinson's disease corresponds to that of the NMDA receptor antagonist CPP. While budipine does not induce ipsilateral or contralateral rotations when given alone, it potentiates the action of dopaminergic drugs, such as apomorphine and lisuride (Löschmann et al., 1991). (2) Budipine selectively prevents NMDA-induced seizures at doses which are effective in models of Parkinson's disease. (3) Budipine prevents NMDA-induced release of acetylcholine in rabbit caudate nucleus slices in a noncompetitive way (Jackisch et al., 1994). (4) Budipine has weak affinity for the phencyclidine site of the NMDA receptor. Inhibition of [^{3}H]TCP-binding, however, occurred at a concentration of 36 μM which exceeds the brain tissue concentration present under in vivo conditions. The available pharmacokinetic data suggest that the peak brain tissue concentration in rats after a single effective dose of budipine (10 mg/kg i.p. or i.v.) is ~ 8 μM (Zech et al., 1985). The seizure experiments show that budipine exerts a specific NMDA receptor antagonistic action in vivo. In addition, effective inhibition of NMDA-evoked acetylcholine release was observed at a concentration of 4.6 μM, suggesting that budipine – although it interacts with the NMDA receptor-linked ion channel – does not affect directly the site to which phencyclidine binds (Jackisch et al., 1994).

Olney et al. (1987) have shown that conventional antimuscarinic antiparkinson drugs, such as biperiden, prevent NMDA receptor-mediated excitotoxicity and possess weak affinity for the phencyclidine-binding site of the NMDA receptor. Similarly, budipine might be an antimuscarinic compound with an additional anti-NMDA action. Direct comparison of the actions of budipine and biperiden, however, reveals a number of differences. Depending on the paradigm used, the antimuscarinic effect of budipine is 20–150 × weaker than that of biperiden (Menge and Brand, 1985). In in vivo models of Parkinson's disease, however, budipine and biperiden are effective at comparable doses, suggesting that the antimuscarinic properties of budipine cannot account for its antiparkinsonian action. Compared with biperiden, budipine has 4–5-fold higher affinity for the phencyclidine-binding site within the NMDA receptor complex. In addition, our seizure experiments demonstrate an in vivo anti-NMDA action of budipine, but not of biperiden.

In conclusion, the present data suggest that the novel antiparkinson drug budipine mainly acts by blocking muscarinic and NMDA transmission while facilitation of dopaminergic transmission does not appear to contribute to its in vivo action. In comparison to biperiden, the anti-NMDA properties of budipine are more prominent. Clinical experience shows that budipine is particularly useful in patients whose tremor is not sufficiently relieved by levodopa and dopaminergic agonists. We have recently observed that the competitive NMDA receptor antagonist 3-[(R)-2-carboxypiperazin-4-yl]-prop-2-enyl-1-phosphonic acid (D-CPPene) suppresses harmaline-induced tremor in mice and rats (Eblen et al., 1995). In addition, the noncompetitive NMDA receptor antagonist memantine has a pref-

erential action on parkinsonian tremor (Schneider et al., 1984). The NMDA receptor antagonistic action of budipine in conjunction with its weak antimuscarinic action probably underlies its pronounced antitremor effect.

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