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Paradoxical anticonvulsant activity of the excitatory amino acid *N*-methyl-D-aspartate in the rat caudate-putamen

(basal ganglia/pilocarpine/seizure/epilepsy/brain damage)

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ABSTRACT **We used limbic seizures induced in rats by systemic injection of the cholinergic agonist pilocarpine (380 mg/kg; i.p.) to study the neuronal pathways within the basal ganglia that modulate seizure threshold. *N*-Methyl-D-aspartate (*N*-Me-D-Asp) is an excitatory amino acid derivative that is a powerful convulsant agent when injected into the cerebral cortex, amygdala, or hippocampus in rats. Bilateral microinjections of *N*-Me-D-Asp into the caudate-putamen, however, protected against limbic seizures induced by pilocarpine (injected systemically), with an ED_{50} of 0.7 nmol (range 0.5–1.0 nmol). Lesioning the caudate-putamen (by bilateral microinjection of the excitotoxin ibotenate) converted subconvulsant doses of pilocarpine into convulsant ones. The anticonvulsant action of *N*-Me-D-Asp in the caudate-putamen was reversed by blocking γ-aminobutyrate-mediated inhibition in the substantia nigra pars reticulata or in the entopeduncular nucleus. The results suggest that the caudate-putamen and its γ-aminobutyrate-dependent efferent pathways modulate the threshold for seizures in the limbic forebrain.**

The function of the basal ganglia in the spread of seizures within the forebrain has interested neurologists, neurosurgeons, and neuropathologists since the 19th century (1). Clinical observations in humans and lesion studies in monkeys and dogs established that the globus pallidus (GP) and the substantia nigra (SN) serve as relay stations in the propagation of seizures elicited from the motor cortex or the limbic system (2, 3). However, the precise pathways in the basal ganglia that are involved in the spread of seizures and the specific neurotransmitters used in these pathways have not been identified.

The SN has been proposed as a key site at which the anticonvulsant activity of drugs that enhance γ-aminobutyric acid (GABA)-mediated inhibition is expressed (4, 5). Excitation within the SN is probably mediated by dicarboxylic amino acids (L-glutamate or L-aspartate). Blockade of excitatory neurotransmission in the SN by 2-amino-7-phosphonoheptanoate, an antagonist that acts selectively at the receptor site sensitive to *N*-methyl-D-aspartate (*N*-Me-D-Asp), raises the threshold for seizures and curtails their motor expression (6, 7).

Temporal lobe, or "psychomotor," epilepsy is the most common form of epilepsy in humans (8). Prolonged limbic seizures in animals and humans result in selective damage to the forebrain, involving hippocampus, amygdala, and sometimes the thalamus (9). This form of epilepsy is particularly resistant to anticonvulsant medication and represents a major therapeutic problem (10).

Seizures produced by pilocarpine in rats provide an animal model of temporal lobe epilepsy that permits the evaluation of behavioral, electroencephalographic, and morphological sequelae of intractable limbic convulsions (11–13). This experimental model of epilepsy serves to delineate the anatomical substrates essential for the motor expression of seizures (7, 14).

We recently observed that microinjections of the GABA agonist muscimol or an irreversible inhibitor of GABA transaminase, γ-vinyl-GABA, into the rat substantia nigra pars reticulata (SNR) or entopeduncular nucleus (EP) protect against the convulsant action of pilocarpine (14, 15). These findings suggested that GABAergic afferents to the SNR and to the EP produce an anticonvulsant action. We now present evidence that pathways linking the striatum and either SNR or EP may regulate the seizure threshold of the limbic forebrain. We have observed alterations in the behavioral, electroencephalographic, and morphological sequelae of seizures produced by pilocarpine following the bilateral microinjection of *N*-Me-D-Asp into different subregions of the rat caudate-putamen, nucleus accumbens, and GP.

MATERIALS AND METHODS

Male Wistar rats (230–250 g) were anesthetized with sodium pentobarbital (Nembutal; Ceva, Watford, UK; 50 mg/kg, i.p.) and chronically implanted with guide cannulae directed toward the caudate-putamen, nucleus accumbens, GP, SNR, and EP. Coordinates for microinjections into the caudate-putamen, nucleus accumbens, GP, SNR, and EP, derived from the atlas of König and Klippel (16), were as follows. Caudate-putamen A 9410: AP 9.41, L 1.0 to 2.6, V +2.0 to 0.6. Caudate-putamen A 7890: AP 7.89, L 1.0 to 3.6, V −1.0 to +2.2. Caudate-putamen A 6360: AP 6.36, L 2.0 to 4.5, V −1.6 to +2.0. Nucleus accumbens: AP 9.41, L 0.6 to 1.6, V −1.0 to 0.0. GP: AP 6.36, L 2.0 to 3.0, V −1.6 to +0.2. SNR: AP 1.61, L 1.9, V −2.6. EP: AP 4.89, L 2.4, V −1.8. The microinjections into the caudate-putamen, nucleus accumbens, GP, SNR, and EP were performed bilaterally in unanesthetized rats. The drugs were delivered into the caudate-putamen, nucleus accumbens, and GP in a volume of 0.5 μl at a rate of 0.1 μl/min and into the SNR and EP in a volume of 0.2 μl at a rate of 0.04 μl/min. *N*-Me-D-Asp (Tocris, Buckhurst Hill, Essex, UK) was administered bilaterally into the caudate-putamen in doses of 0.1, 0.5, 1, and 2 nmol. 2-Amino-7-phosphonoheptanoate (Tocris) was micro-

Abbreviations: *N*-Me-D-Asp, *N*-methyl-D-aspartate; GABA, γ-aminobutyrate; SN, substantia nigra; SNR, substantia nigra pars reticulata; EP, entopeduncular nucleus; GP, globus pallidus.

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injected into the caudate-putamen in the dose of 5 nmol, 15 min before i.p. injection of pilocarpine hydrochloride (Sigma; 380 mg/kg). *N*-Me-D-Asp (2 nmol) and 2-amino-7-phosphonoheptanoate (2 nmol) were coadministered into the ventral part of the caudate-putamen 15 min before pilocarpine (380 mg/kg). Bicuculline methiodide (Pierce) was administered bilaterally into the SNR in doses of 10 and 50 pmol or into the EP in the dose of 10 pmol. Ibotenic acid (Sigma; 30 nmol) was microinjected bilaterally into the caudate-putamen (A 7890) at coordinates AP 7.89, L 2.6, V +1.4 and −0.6 (17). The drug was delivered in a volume of 0.5 μl at a rate of 0.1 μl/min. After surgery, animals were housed individually and were allowed to recover for a period of 10–14 days (17). Methylscopolamine nitrate (Sigma; 1 mg/kg) was administered s.c. 30 min before injection of pilocarpine, to limit peripheral toxic effects (11). *N*-Me-D-Asp, 2-amino-7-phosphonoheptanoate, and ibotenic acid were dissolved in 1 M NaOH, and the solutions were diluted with 0.9% NaCl (pH adjusted to 7.35 with 0.2 M HCl). Pilocarpine, methylscopolamine, and bicuculline methiodide were dissolved in 0.9% NaCl. No rats were used for more than one microinjection. The dose of *N*-Me-D-Asp administered into the caudate-putamen and required to block the seizure response in 50% of rats (ED_{50}; effective dose) given pilocarpine (380 mg/kg) was determined by computer analysis of the data obtained from four experiments with different dosages. The criterion used to indicate convulsive response was status epilepticus defined as continuous motor limbic seizures [stage 5 according to Racine (18)] for a period longer than 30 min. The incidence of seizure response (probit transformed percentages) was plotted vs. the logarithm of the dose of *N*-Me-D-Asp administered into the caudate-putamen. The ED_{50} and the confidence limits were estimated by fitting the data by linear regression analysis (19).

For electroencephalographic recordings (Beckmann model RM polygraph, time constant 0.03 sec, high cut-off filter 15 Hz), bipolar twisted electrodes (tip diameter 100 μm, interelectrode distance 500 μm) were positioned in the dorsal hippocampus [AP 4.0, V +2.6, L 1.7 (16)]. Surface recordings were led from screws positioned bilaterally over the occipital cortex. The correct location of the implanted deep electrodes was histologically controlled in serial sections stained with cresyl violet.

The brains were processed for morphological examination by light microscopy 1–3, 5–15, or 21–45 days after administration of pilocarpine. The rats were anesthetized with an overdose of sodium pentobarbital and perfused with a fixative containing 10% acetic acid, 10% formaldehyde, and 80% methanol. The brains were allowed to fix *in situ* at 4°C for 24 hr and then were removed and processed for paraffin embedding. Subsequently, serial sections of the entire brain were cut coronally at 10 μm, and every 10th section was mounted on a glass slide and stained with cresyl violet or according to the Fink and Heimer technique (20).

RESULTS

Microinjections of *N*-Me-D-Asp into the ventral part of the caudate-putamen (A 7890) protected rats against seizures produced by pilocarpine (380 mg/kg), with an ED_{50} of 0.7 nmol (range 0.5–1.0 nmol; $n = 29$). The dose of 2 nmol was selected for delineation of the topography of anticonvulsant action of *N*-Me-D-Asp, since this dose in the ventral caudate-putamen (14 of 14 rats) led to total blockade of seizures induced by pilocarpine (380 mg/kg). No clear-cut protective effect of *N*-Me-D-Asp (2 nmol) occurred after microinjection in the anterior (A 9410) (6 of 12 rats) or dorsal (A 7890) (6 of 14 rats) part of the caudate-putamen. Microinjections of *N*-Me-D-Asp (2 nmol) into the ventral part of the caudate-putamen (A 7890) (14 of 14 rats) and posterior caudate-putamen (A 6360) (9 of 10 rats) conferred protection against pilocarpine-induced seizures (Fig. 1). Microinjections of *N*-Me-D-Asp (2 nmol) into the nucleus accumbens ($n = 4$) and GP ($n = 7$) did not result in an anticonvulsant effect (Fig. 1).

Electrographic monitoring showed that microinjections of *N*-Me-D-Asp (2 nmol) into the ventral and posterior caudate-putamen blocked the development of seizure activity produced by pilocarpine (380 mg/kg) ($n = 13$) (Fig. 2). Microinjections of *N*-Me-D-Asp (2 nmol) ($n = 7$) into the anterior and dorsal caudate-putamen did not alter the development of seizures as revealed by electroencephalography. Morphological analysis of the brains revealed definite protection against the seizure-related brain damage after microinjections of *N*-Me-D-Asp (2 nmol) into the ventral and posterior caudate-putamen (Fig. 1). The anticonvulsant effect of *N*-Me-D-Asp in the ventral part of the caudate-putamen (A 7890) was reversed by coadministration of 2 nmol of the specific *N*-Me-D-Asp antagonist 2-amino-7-phosphonoheptanoate ($n = 5$). Microinjections of 5 nmol of 2-amino-7-phosphonoheptanoate into the ventral part of the caudate-putamen, 15 min prior to systemic administration of pilocarpine (380 mg/kg), led to the rapid development of status epilepticus and to the death of all five animals tested within 10–30 min. Microinjections of saline into different

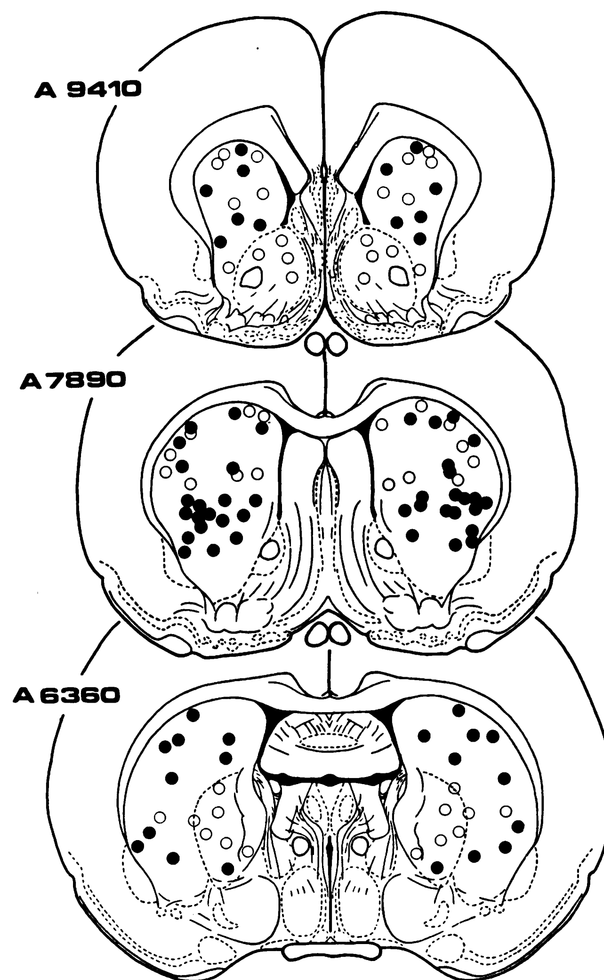

FIG. 1. Schematic reconstruction of injection sites of *N*-Me-D-Asp in the caudate-putamen, nucleus accumbens, and GP from serial coronal sections of perfused rat brain. *N*-Me-D-Asp (2 nmol) was microinjected bilaterally into the caudate-putamen 15 min before i.p. administration of pilocarpine (380 mg/kg). Dark circles represent sites from which *N*-Me-D-Asp protects rats from seizures produced by pilocarpine. Open circles represent sites from which *N*-Me-D-Asp does not alter the convulsant action of pilocarpine.

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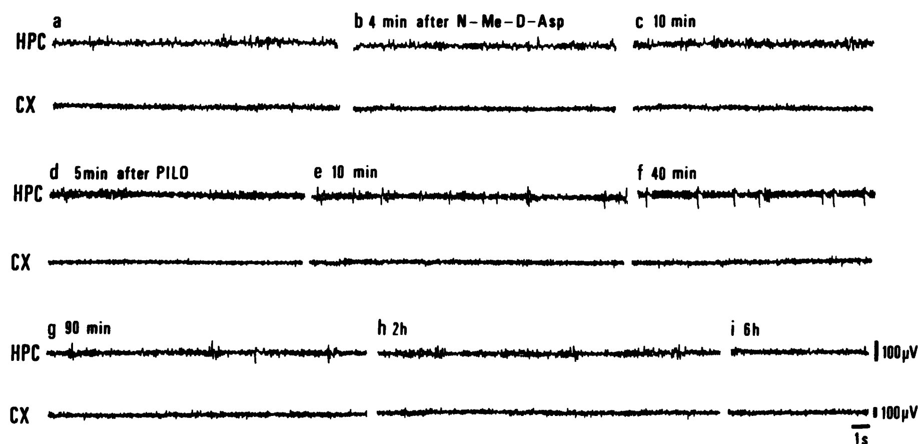

FIG. 2. Electrographic recordings from the hippocampus (HPC) and cortex (CX), demonstrating the effect of microinjection of *N*-Me-D-Asp (2 nmol), bilaterally, into the ventral part of the caudate-putamen (A 7890) on the convulsant action of pilocarpine (PILO, 380 mg/kg) given i.p. 15 min later. (*a*) Pre-drug control recordings. (*b* and *c*) Unchanged records 4 and 10 min after microinjection of *N*-Me-D-Asp into the caudate-putamen. (*d*) Theta rhythm and low-voltage fast activity prevail in hippocampal recordings and cortex 5 min after the injection of pilocarpine. (*e*) High-voltage fast activity and spikes in the hippocampus supersede the pre-drug background activity 10 min after administration of pilocarpine. (*f*) Isolated spikes registered exclusively in the hippocampal record and low-voltage fast activity prevail in the electroencephalogram 10–90 min after administration of pilocarpine. (*g*) High-voltage spiking progressively builds up in the hippocampal recording and disappears after a delay of 1–2 hr after the injection of pilocarpine. (*h*) By 1.5–2 hr after injection of pilocarpine, the electroencephalogram progressively normalizes in both hippocampal and cortical recordings. (*i*) By 4–6 hr after injection of pilocarpine the electroencephalogram returns to the pre-drug patterns. Control electroencephalographic recordings in animals receiving only pilocarpine (380 mg/kg) were similar to those illustrated in Figs. 3 and 4.

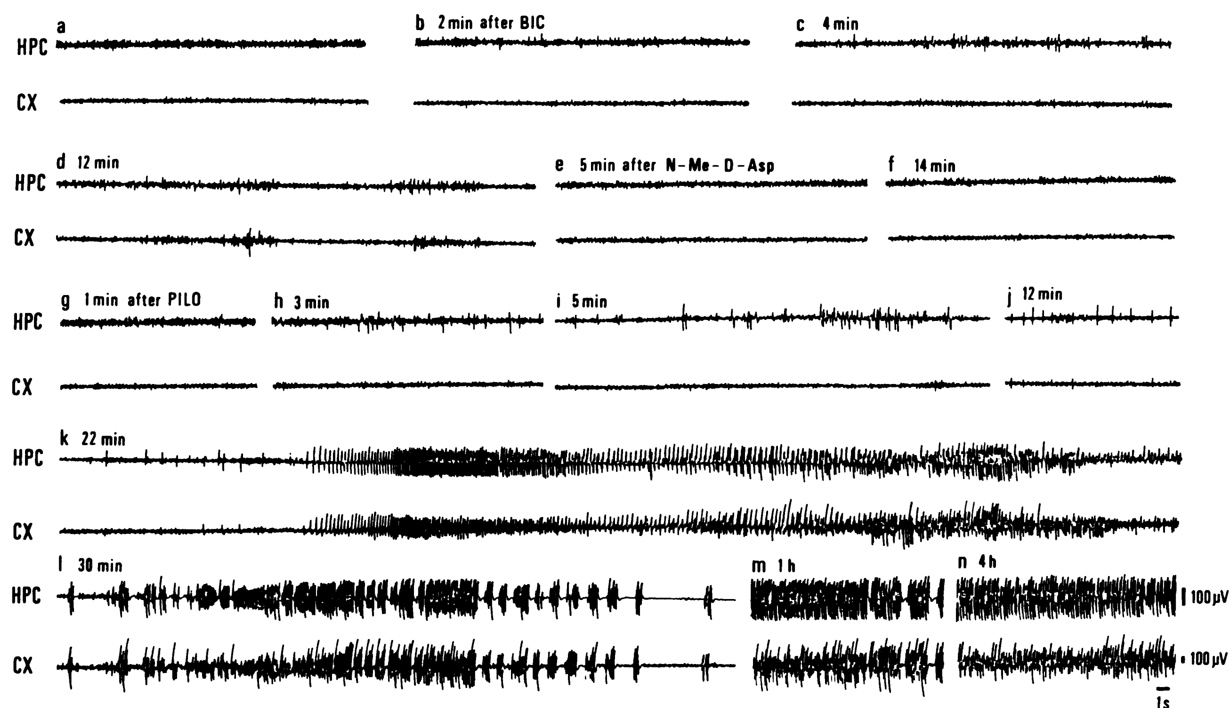

FIG. 3. Microinjection of bicuculline methiodide (BIC) into the EP reverses anticonvulsant action of *N*-Me-D-Asp in the caudate-putamen. Bicuculline methiodide (10 pmol) was microinjected into the EP, bilaterally, 15 min before injection of *N*-Me-D-Asp (2 nmol) into the ventral part of the caudate-putamen (A 7890). Fifteen minutes later, the animal received pilocarpine (PILO, 380 mg/kg i.p.). (*a*) Pre-drug control recordings. (*b*) The background activity in the hippocampus is replaced with high-voltage fast activity and spiking within 1–2 min after injection of bicuculline methiodide into the EP. (*c* and *d*) High-voltage spiking spreads to cortical recordings. (*e* and *f*) Microinjection of *N*-Me-D-Asp into the ventral part of the caudate-putamen rapidly normalizes the hippocampal and cortical recordings. (*g*) Significant theta rhythm in the hippocampus and fast activity in the cortex registered 1 min after injection of pilocarpine. (*h* and *i*) High-voltage fast activity superposes over hippocampal theta rhythm and progresses into the high-voltage spiking registered initially in hippocampal recordings. (*j*) High-voltage spiking represents the characteristic pattern of the electroencephalogram registered by 10–15 min after administration of pilocarpine. Low-voltage fast activity and isolated spikes are registered in the cortex concurrently to the hippocampal patterns. (*k*) High-voltage spiking registered initially in the hippocampus precedes the development of the first electrographic seizure, registered 22 min after injection of pilocarpine. (*l*) Electrographic seizure registered 30 min after injection of pilocarpine. Ictal periods recur every 5–8 min and result in a status epilepticus within 40–50 min after pilocarpine injection. (*m* and *n*) Electrographic activity during the status epilepticus 1 and 4 hr after pilocarpine administration. Progressive normalization of the electrographic activity is observed within 16–24 hr post-injection. Electroencephalographic activity returns to the pre-drug pattern within 48 hr, although isolated spikes are registered in both recordings up to 3–5 days after injection of pilocarpine. HPC, hippocampus; CX, cortex.

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parts of the caudate-putamen (n = 6) did not affect seizures produced by pilocarpine (380 mg/kg).

To characterize the pathway specificity of the anticonvulsant action of *N*-Me-D-Asp in the caudate-putamen, eight rats were injected with *N*-Me-D-Asp (2 nmol) into the ventral part of the nucleus (A 7890) and subsequently given pilocarpine (380 mg/kg). One week later, ibotenate (60 nmol) was microinjected into the caudate-putamen at the same coordinates from which an anticonvulsant effect of *N*-Me-D-Asp was achieved. After 2 weeks of recovery, pilocarpine (250 mg/kg) was injected in these animals. Five out of eight lesioned rats developed typical limbic seizures and status epilepticus that resulted in seizure-related brain damage in response to this dose of pilocarpine. In sham-operated rats (n = 6), pilocarpine (250 mg/kg) was nonconvulsant.

To characterize the neurotransmitter specificity of the anticonvulsant action of *N*-Me-D-Asp in the caudate-putamen and the proconvulsant effects of caudate-putamen lesions with ibotenate, we examined whether blockade of GABAergic transmission within the SNR and EP attenuates the anticonvulsant effect of *N*-Me-D-Asp. Bicuculline methiodide (10 or 50 pmol) was given bilaterally into the SNR (n = 7) or EP (n = 6) 15 min before microinjection of *N*-Me-D-Asp (2 nmol) into the ventral caudate-putamen and 30 min before injection of pilocarpine (380 mg/kg). The protective effect of *N*-Me-D-Asp microinjection in the ventral part of the caudate-putamen was abolished by microinjection of bicuculline into either SNR or EP, as judged by behavioral (n = 13) and electroencephalographic (n = 10) (Figs. 3 and 4) monitoring and morphological analysis.

DISCUSSION

The results show that an increase in the net excitation in the caudate-putamen results in an anticonvulsant effect. An anticonvulsant effect of *N*-Me-D-Asp in the rat caudate-putamen was detectable throughout the entire extent of the nucleus. However, the predominant effect was elicited from the ventral and posterior part of the caudate-putamen. Microinjections of *N*-Me-D-Asp into the caudate-putamen not only blocked the motor expression of pilocarpine-induced seizures but also prevented the evolution of paroxysmal electrographic activity in the hippocampus and cortex, as well as totally prevented the seizure-related brain damage. Furthermore, chemical lesions destroying the output neurons located in the medial part of the caudate-putamen lowered the threshold for seizures produced by pilocarpine.

The anticonvulsant effect of *N*-Me-D-Asp in the caudate-putamen was abolished by blockade of GABA-mediated inhibition in the SNR and EP (nuclei receiving efferent projections from the caudate-putamen). These observations suggest that excitatory amino acid neurotransmission within the caudate-putamen modulates the seizure threshold of the limbic system, and they define the striatal output pathways that are responsible for this effect. These findings form an interesting parallel to electrical-stimulation studies that indicated a possible role for the caudate nucleus in the control of convulsive activity in the amygdala, hippocampus, and temporal cortex in cats and dogs (21). The equal potency of the blockade of GABAergic input to the SNR and EP in attenuating the effect of *N*-Me-D-Asp in the caudate-putamen

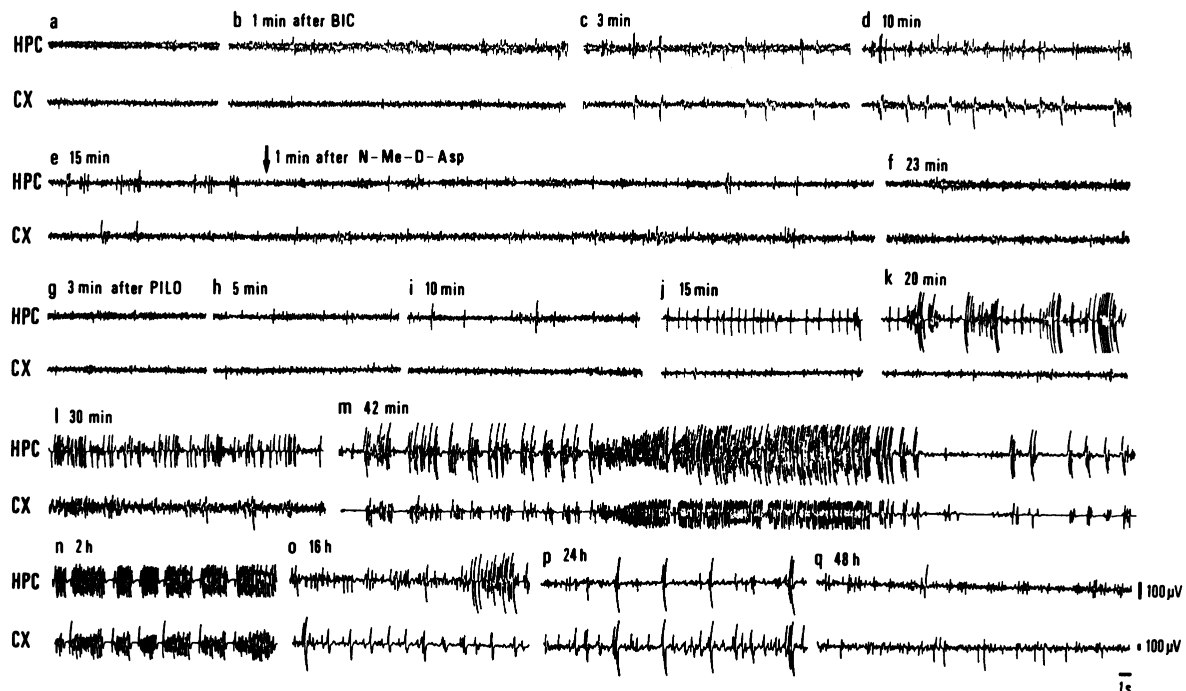

FIG. 4. Microinjection of bicuculline methiodide (BIC) into the SNR reverses anticonvulsant action of *N*-Me-D-Asp in the caudate-putamen. Bicuculline methiodide (50 pmol) was microinjected into the SNR, bilaterally, 15 min before injection of *N*-Me-D-Asp (2 nmol) into the ventral part of the caudate-putamen (A 7890). Fifteen minutes later, the animal received pilocarpine (PILO, 380 mg/kg i.p.). (*a*) Pre-drug control recording. (*b*) The background activity is replaced with high-voltage fast activity 1–2 min after microinjection of bicuculline methiodide into the SNR, while cortical recordings display no alterations. (*c* and *d*) High-voltage fast activity and spiking prevail in hippocampal and cortical recordings 3–15 min after microinjection of bicuculline methiodide into the SNR. (*e* and *f*) Microinjection of *N*-Me-D-Asp into the ventral part of the caudate-putamen rapidly normalizes the hippocampal and cortical electroencephalograms. (*g*) Significant theta rhythm is registered in the hippocampus 3–5 min after injection of pilocarpine. (*i–k*) High-voltage fast activity (*i*) with spiking (*j*) and bursts of polyspiking (*k*) prevail in hippocampal recordings 10–20 min after injection of pilocarpine. (*l*) High-voltage spiking and fast activity become synchronized in the hippocampus and cortex. (*m*) Prominent high-voltage spiking precedes the first electrographic seizure, registered 42 min after injection of pilocarpine. (*n*) Electrographic activity registered 1–8 hr after injection of pilocarpine, during status epilepticus. (*o*) By 8–24 hr after injection of pilocarpine, the electroencephalogram progressively normalizes. (*p* and *q*) Highly synchronized isolated spikes are registered 24–48 hr post-injection. The electroencephalogram returns to the pre-drug patterns 3–7 days after pilocarpine injection. HPC, hippocampus; CX, cortex.

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argues against a preferential role for the SN in gating the expression of seizure activity.

The SN and EP both undergo irreversible degeneration in rats subjected to status epilepticus, whereas striatum is resistant to epilepsy-related cell damage (9, 22). Similarly, the caudate-putamen is remarkably resistant to the generation of kindled seizures (18). Excitatory neurotransmission in the caudate-putamen, the SN, and the EP participates in the regulation of the final set-point of the respective output neurons, thus providing modulation of the passage of information through the basal ganglia (23). Excitatory neurotransmission in the basal ganglia is involved in the fine processing of the sensory and motor information required for integration of the neocortex, limbic forebrain, and spinal motor centers.

The basal ganglia provide a center for communication between the sensorimotor cortex and the limbic system and thus participate both in the propagation of motor seizures to the executive targets and in the generation of the seizure activity within the limbic centers.

Our findings demonstrate that both of these aspects of epileptogenesis are subject to control by excitation and inhibition within the striatum and its efferent pathways.

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