Activation of Substantia Nigra Neurons: Role in the Propagation of Seizures in Kindled Rats

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The substantia nigra (SN) is crucial to the propagation of seizures in kindled rats and in other experimental seizure models. However, the mechanisms by which the SN acts to facilitate the propagation of seizures are unknown. To investigate these mechanisms we (1) quantified the activity of SN neurons during seizures in kindled and naive rats in a paralyzed, ventilated state and (2) examined the relationship between activity of neurons in the SN and the seizure-facilitating action of this structure. Our principal findings were that (1) the majority of both SN dopamine and SN pars reticulata neurons, in kindled rats, fired in bursts temporally correlated to EEG waveforms recorded outside the SN during seizures; (2) this response was only rarely found in SN neurons of naive rats during seizures elicited by stimulation of the amygdala; (3) unlike kindled rats, lesions of the SN in naive rats did not suppress seizures.

The finding that SN neurons fired in bursts during seizures in kindled, but not naive, rats indicates that seizure activity propagated into SN only in kindled rats. The correlation between seizure-suppressant effects of lesions and SN activation during seizures leads us to propose that one mechanism by which the SN promotes seizure propagation involves SN activation and transmission of seizure activity to targets of SN.

Kindling is an animal model of epilepsy (for a review, see McNamara et al., 1985). The term "kindling" refers to a phenomenon in which repeated administration of an initially subconvulsive electrical stimulus eventually results in intense limbic and clonic motor seizures (Goddard, 1967). In rats kindled by repeated stimulation of the amygdala, the initial stimulus evokes only a brief focal electrical seizure, termed "afterdischarge" (AD), without behavioral manifestations. Once established, the enhanced response to the initially subconvulsive stimulus is permanent (Goddard et al., 1969).

Several lines of evidence indicate that the substantia nigra (SN) is crucial to the propagation of seizures in both kindled animals and other experimental models. Microinjection of muscimol, a GABA agonist, or gamma-vinyl GABA, a GABA-transaminase inhibitor, into the SN, but not dorsal to the SN, suppresses both electrically and chemically induced seizures (Gonzalez and Hettinger, 1984; Iadarola and Gale, 1982; Le

Gal la Salle et al., 1983; McNamara et al., 1983, 1984). This anticonvulsant action is apparently mediated by suppression of neuronal activity in the SN, since microinjection of muscimol suppresses nigral unit activity (Waszczak et al., 1980) and also suppresses nigral output to superior colliculus (Hikosaka and Wurtz, 1985). The fact that destruction of the SN also protects against seizures (Garant and Gale, 1983; McNamara et al., 1984) further supports the idea that the anticonvulsant action is mediated by suppression of nigral neuronal activity.

These findings indicate that the SN facilitates the propagation of seizures, but they do not specify a mechanism of action. The SN may itself transmit seizure activity from rostral sites of origin to target structures. Alternatively, the SN, by means of its basal activity, may provide a tonic seizure-facilitating action on other pathways, through which the seizure is transmitted. We initiated investigations of these possibilities by recording single-unit activity of neurons in the SN through the course of electrically induced seizures in both naive and kindled rats. The findings of the single-unit studies led us to examine the effects of SN lesions on electrically induced seizures in the amygdala of naive rats.

Materials and Methods

Stereotactic surgery

Male Sprague-Dawley rats (Charles River Breeding Laboratories) were anesthetized with pentobarbital. A bipolar stimulating electrode was placed in the right amygdala, a monopolar electrode for recording electroencephalographic (EEG) activity was placed in the right caudate, and an indifferent EEG reference source was obtained from a lead connected to a screw placed in the skull, as previously described (McNamara et al., 1984).

Kindling

Animals were maintained on a light (0700–1900)/dark (1900–0700) cycle. After a postoperative recovery period of at least 4 d, constant-current stimulations (300–1000 μA, 1 msec, biphasic square wave pulses, 60 Hz for 1 sec) were delivered to the amygdala 5–7 times/d at interstimulus intervals of at least 90 min. Animals were stimulated 7 d a week until 3 consecutive stimulations evoked a clonic motor seizure with rearing and falling (class 5 seizure, as described by Racine, 1972). A second group of animals was implanted with electrodes but not stimulated and was used as a naive control group.

Extracellular recording

Not less than 5 d after completion of kindling, animals were anesthetized with halothane and a cannula was inserted into the trachea. The animals were ventilated at a rate that maintained CO_2 concentrations in the expired air at 3.5–4.5%, as determined with an Infrared Products CO_2 monitor. Body temperatures were maintained near 37°C, using a temperature probe and an adjustable heating pad. While the rats were under halothane anesthesia, a burr hole was drilled in the skull overlying the

left SN (3 mm anterior to lambda, 2 mm left of the central suture). Infiltration anesthesia (5–7 ml of 1.5% mepivacaine) was administered to all wound edges and pressure points. Animals were then paralyzed by tail vein injection of 0.3 ml of gallamine (20 mg/ml) and ventilated with room air.

We emphasize that all surgical procedures were carried out under halothane anesthesia and that all animals were treated with the long-acting infiltration anesthetic, mepivacaine. Recording sessions typically lasted 2.5 hr or less. In paralyzed animals prepared exactly as described above, heart rate (377.2 ± 25.9 beats/min; $n = 5$) and mean arterial pressure (116.0 ± 6.3 mm Hg; $n = 5$) gave no indication of undue stress, since these values fall within the normal range for untreated animals (Baker et al., 1979). These procedures were carried out in accordance with the guidelines for the care and use of laboratory animals established by the Institute of Laboratory Animal Resources (Moreland et al., 1978).

Extracellular single-unit recordings were made from SN neurons using glass pipette electrodes containing a thread of fiberglass and filled with 2.0% pontamine blue in 2 M NaCl (4–6 MΩ). Recordings were made from SN dopamine neurons and SN pars reticulata neurons (SNPR) tentatively identified on the basis of their waveform, firing rate, and location (Grace and Bunney, 1983; Guyenet and Aghajanian, 1978). Amplitude of the SN units was at least twice, and more typically 4 times baseline noise (Fig. 1).

Once a SNPR or a SN dopamine neuron was isolated, an electrical seizure was evoked by stimulating the contralateral amygdala (1000 μA 1 msec pulses at 60 Hz for 2 sec). No more than 6 ADs were evoked in any one animal during single-cell recording. The interval between AD-evoking stimulations was always at least 10 min. In 4 cases the same cell was followed through multiple ADs. In all other cases, a different cell was selected prior to each evoked seizure. To determine whether electrical stimulation of the amygdala without associated AD would alter the firing rate of SN neurons, animals were stimulated with trains of electrical stimulation at current intensities insufficient to evoke AD (1 msec pulses, 60 Hz, for 2 sec) or with single pulses of current at intensities that would evoke AD if given in a train (1000 μA, 1 msec, biphasic square wave).

To test whether the activities observed in the SN of kindled animals were common to all brain stem cells, we recorded unit activity of neurons located in pontine reticular formation caudal to the SN (0–1.3 mm posterior to lambda, 1.0–1.3 mm right of the central suture) at approximately the same dorsal/ventral level as the SN (7–10 mm from dura). These recordings in kindled rats were performed exactly as described above, except that tungsten microelectrodes (F. Haer; 2–4 MΩ) were used.

Amplified EEG and single-unit signals were recorded on both tape and strip-chart recorders. Rate data were quantified using a Medical Systems International computer or an RC Electronics Computerscope. Examination of tape-recorded data for temporal correlations between nigral unit activity and EEG waveforms was performed by an investigator unaware of the experimental treatment (J.O.M.). The criterion for determining that a cell was firing in a manner temporally correlated to components of the EEG waveform was that the cell fire in bursts of 3 or more action potentials temporally associated with 3 or more consecutive EEG spikes during AD.

Recording sites were marked by iontophoretic dye injection using a DC current of 15 μA for 15 min or, in the case of the metal electrodes, by a marking lesion made by application of 10 sec of 100 μA cathodal current. Animals were killed by a lethal dose of halothane.

Histology

Placements of bipolar stimulating electrodes in the right amygdala, EEG recording electrodes in the right caudate, and unit recording electrodes in the left SN were verified histologically. Brains were removed and stored in a fixative solution of sucrose and formalin, as described previously (Waszczak et al., 1980). Sections 40-μm-thick were cut on a freezing microtome and the location of the dye injection was determined. The sections were then stained for Nissl substance to better determine the location of stimulating and recording electrode tracks.

Animals were removed from the study if histologic evidence for the presence of stimulating electrodes within the amygdala or recording electrodes within the SN could not be obtained.

SN lesion experiments

Stimulating electrodes were placed in the right amygdala of naive Sprague-Dawley rats, as described above. At the time of electrode placement,
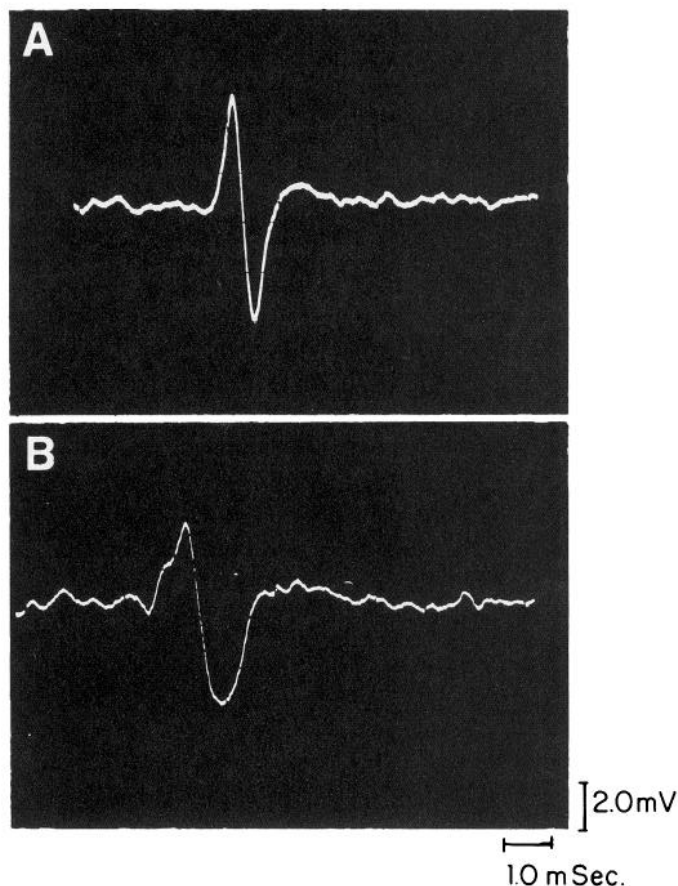

Figure 1. SN neuron waveforms. *A*, Waveform of a neuron recorded in substantia nigra pars reticulata. *B*, Waveform of a neuron recorded in substantia nigra pars compacta. Signals were recorded through a World Precision Instruments amplifier. Low- and high-frequency cutoff filters were 100 and 5000 Hz, respectively.

bilateral lesions of the SN were made by the microinjection of 30 nmol of N-methyl-D,L-aspartate (NMDA) in 0.2 μl saline into each SN. Injections were made at a rate of 0.04 μl/min using a Harvard syringe pump. The injection cannula was removed 2 min after termination of the injection. Control animals received 0.2 μl saline into the SN.

Seven days after surgery, the effect of the nigral lesions on the duration of the evoked afterdischarge (ADD) and the threshold to evoke the AD (ADT) was determined in freely moving animals. ADT was determined by application of an incremental ascending ramp of current levels to the amygdala (100–800 μA, biphasic square wave pulses of 1 msec duration at 60 Hz for 1 sec). Current was incremented in 100 μA steps at intervals of 1 min until an AD was evoked. ADD was determined by inspection of the EEG recorded from the amygdala referenced to a skull screw. The methodology used to assess the effects of nigral lesions on seizure propagation in previously kindled animals has been described in detail elsewhere (McNamara et al., 1984).

Lesion location and size were determined by histologic examination of coronal sections by an investigator unaware of the experimental results (J.O.M.). The cross-sectional area of the nigral destruction in each section was determined using a Videoplan digitizer pad (Carl Zeiss and Summagraphics Corporation). The volume of nigral destruction was then determined by summing the products of the cross-sectional area of destruction and the distance between sections. Only animals with lesions involving at least 25% of each side of the SN were included in the lesioned group.

Statistics

Values reported are the means and standard errors of the mean ($\bar{X} \pm$ SE). Statistical differences between groups were determined using Student's t test, chi-square analysis, or sign tests as appropriate (Armitage, 1971). The level of statistical significance was set at $p < 0.05$.
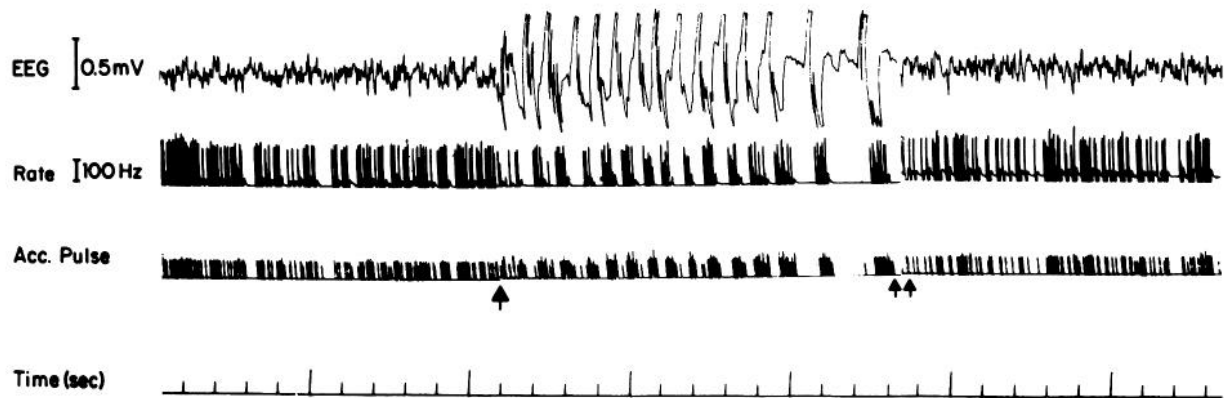
Figure 2. A chart record of caudate EEG and the response of a SNPR neuron during AD evoked in a kindled rat. The *upper trace* is EEG recorded from the caudate; the *second trace* is the instantaneous firing rate of the SN neuron, based on the interval of the 2 most recent action potentials (inverse of interspike interval); the *third trace* is the unit acceptance pulses delivered from the window discriminator to mark the occurrence of an action potential. For graphic presentation, approximately 4 sec of stimulus artifact are excised from each trace (*arrow*). To present activity after termination of the AD, a second cut was made (*double arrow*). The presence of at least 3 action potentials per burst was verified by photographs such as those in Figure 3. It was determined that this cell was firing in bursts temporally correlated to EEG spikes during AD.

Results

Seizure duration in paralyzed rats

AD duration was shorter in the paralyzed than in the unre-strained condition. The AD duration of the final kindled seizure in the freely moving rat was 56 ± 4 sec, compared to 31 ± 7 sec on the first AD subsequently evoked in the paralyzed state ($p < 0.01$). Despite this attenuation of AD duration in the paralyzed state, there was still a statistically significant difference between naive and kindled rats in the AD duration evoked in
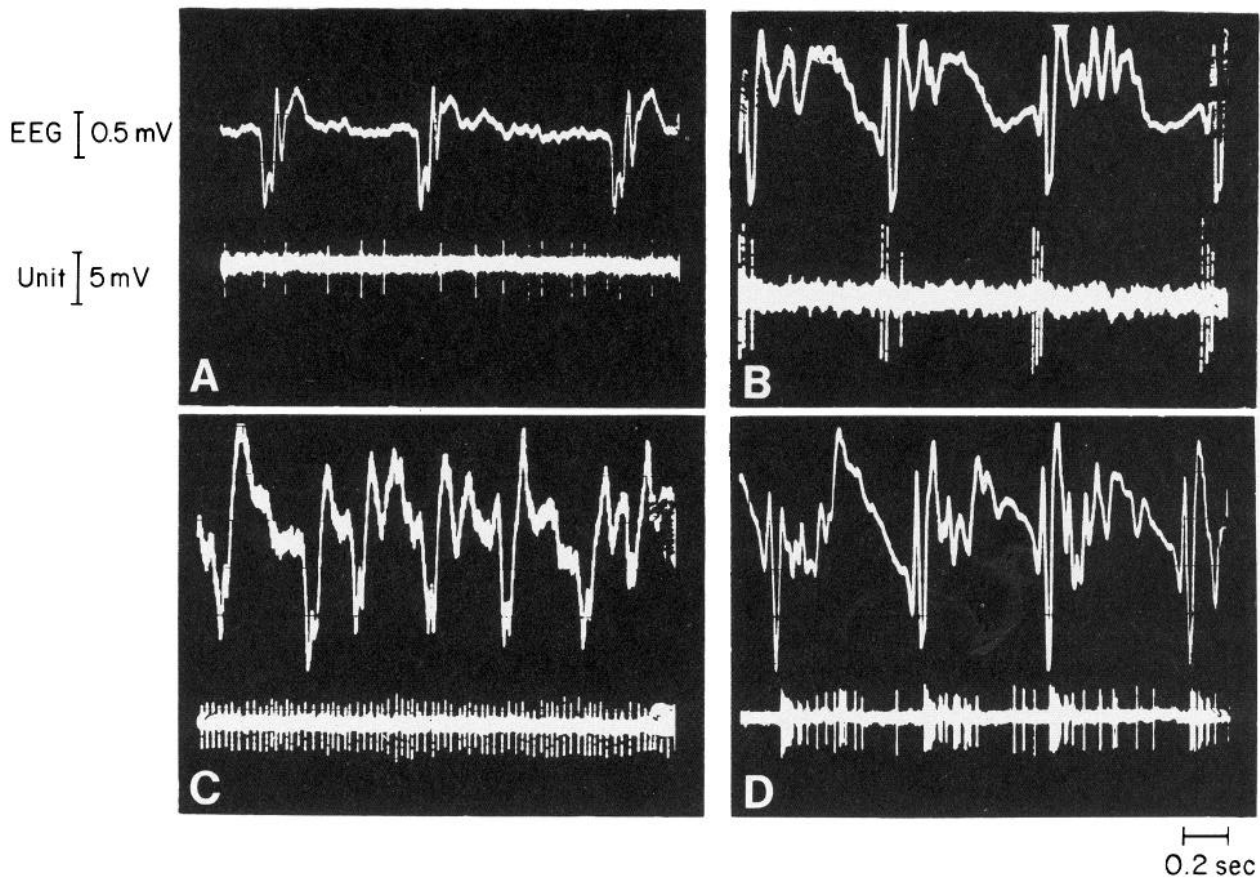

Figure 3. For each set of traces, the *upper trace* is EEG recorded from the caudate during AD, and the *second trace* is the activity of a single SN neuron. *A,* Record from a SN dopamine neuron in a naive rat; it did not change its firing pattern during AD. *B,* Record from a SN dopamine neuron in a kindled rat; it fired in bursts during the spike portion of the EEG AD. *C,* Record from a SNPR neuron in a naive rat; it did not change firing pattern during the AD. *D,* Record of a SNPR neuron in a kindled rat; it was determined to fire in bursts during the spike portion of the EEG during AD.
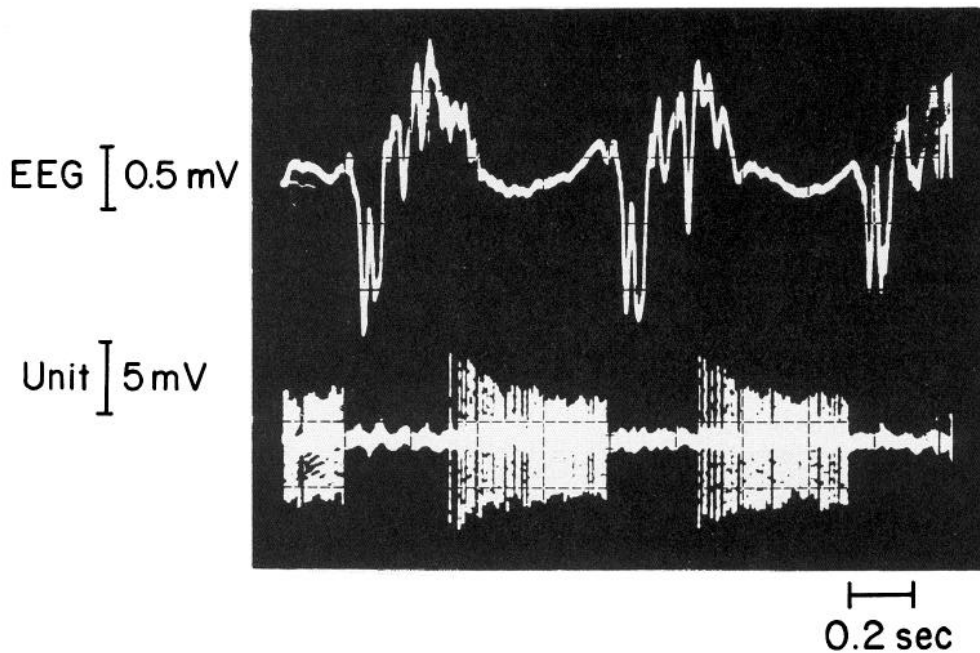
Figure 4. SNPR cell during AD. The *upper trace* is EEG recorded from the caudate during AD. The *second trace* is the unit recording. This neuron was determined to fire in bursts during the slow-wave portion of the AD.

the paralyzed condition. On the first AD evoked in the paralyzed state, AD duration in naive animals was 10 ± 2 sec ($n = 10$), compared to 31 ± 7 sec ($n = 17$) in kindled rats ($p < 0.05$).

Unit activity in the SN: Pattern

Nigral neurons of kindled rats exhibited a striking change in firing pattern during AD. These cells fired in bursts of action potentials with the bursts temporally correlated to waveforms recorded in the EEG (Fig. 2). This change in firing pattern was found in both SNPR and SN dopamine neurons. The likelihood that SNPR units would fire in bursts time-locked to the EEG AD was far greater in kindled rats (86%) than in naive rats (20%) ($p < 0.05$) (Table 1). A similar trend was observed for the relatively few dopamine cells tested ($p < 0.1$) (Table 1, Fig. 3).

The bursts of action potentials generated in the SN during the AD constituted a dramatic change in spike frequency. The interspike interval of the nigral units during the bursts was 5–10 times shorter than the interspike interval of the cell recorded prior to the stimulation. As an example, the within-burst firing rate of the dopamine neuron in Figure 3B (calculated during a typical burst) was 89 spikes/sec, compared to a prestimulus rate of 4 spikes/sec. The within-burst firing rate of the SNPR neuron in Figure 3D was 250 spikes/sec, compared to a prestimulus rate of 25 spikes/sec. The apparent amplitude of the action potential decreased during these bursts.

The bursts of nigral units were temporally correlated to components of the EEG waveform recorded outside the SN (caudate or amygdala). Most nigral units were found to be correlated to the polyspike complex of the EEG during AD (Fig. 3, B, D). However, a minority of the SN cells were clearly correlated to the slow-wave portion of the AD (Fig. 4, Table 1). Cells held through multiple ADs were found to be time-locked to the same component of the waveform on each stimulation. In all cases, the burst-firing pattern terminated at the end of the recorded AD. Distortion of EEG waveforms at fast playback speeds precluded a more precise determination of the temporal relationship between the bursts of action potentials in the SN and individual spikes in the EEG waveform.

The bursting pattern almost always began at some point after the cessation of the stimulus train. Of all the cells recorded, only 2 began to fire in a burst pattern during the stimulus train. The

latency from the time of onset of the AD to the time at which the cell began to fire in bursts varied from 0 to 30 sec.

Despite the observation that the burst-firing pattern became more intense throughout the course of the seizure (Fig. 5), the difference between naive and kindled rats regarding the likelihood that a nigral unit would fire in bursts time-locked to the EEG AD was not merely a function of differences in AD duration. During the initial 10 sec of AD, 17% of the SNPR cells in naive rats were found to be firing in a bursting pattern, whereas, in this same time frame, 65% of the SNPR cells in kindled rats were firing in the bursting pattern.

The burst-firing response of nigral units in kindled rats was not a phenomenon common to all cells in the ventral brain stem. Nigral neurons firing in bursts temporally correlated to the EEG waveform were located throughout the rostral/caudal extent of the SN. On the other hand, of 15 cells recorded in the

Table 1. Temporal correlation of nigral unit activity to EEG during AD

Animal	Fraction of cells bursting time-locked with the AD	No. bursting on EEG spike	No. bursting on EEG slow wave
Naive dopamine	2/6	1	1
Kindled dopamine	7/9	6	1
Naive SNPR	3/15*	3	0
Kindled SNPR	19/22	17	2
Kindled reticular formation	1/15	1	0

The denominator in the fractions presented is the total number of cells within the group examined for burst-firing time-locked to the AD. The numerator is the number of cells found to burst time-locked with the EEG AD.

* A statistically significant difference between naive and kindled rats in the proportion of cells bursting synchronously with the AD ($p < 0.05$; chi-square). SNPR cells were more likely to fire in bursts during the EEG spikes than during the slow waves ($p < 0.01$; sign test). Cells were included in this table only if they were held through the entire course of the AD.
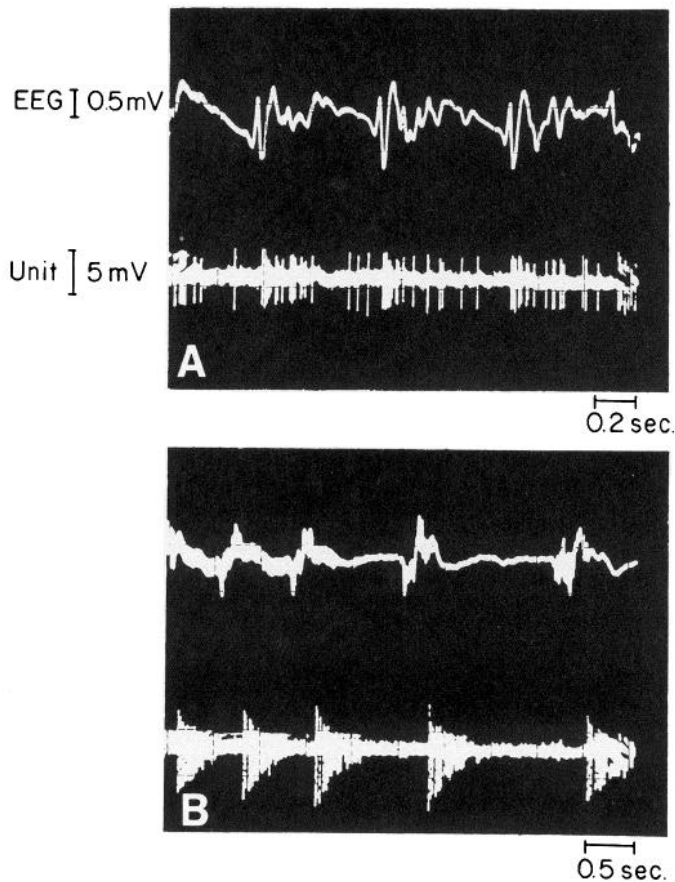
Figure 5. A, SNPR cell during the initial 10 sec of AD. B, The same cell recorded 15 sec later in the same AD. In each case, the *upper trace* is EEG recorded from the caudate and the *lower trace* is the unit recording.

pontine reticular formation caudal to the SN, only 1 cell was found to fire in bursts during the AD (Table 1).

Unit activity in the SN: Rate

No systematic attempt was made to evaluate the baseline firing rates of SN cells in the absence of electrical stimulation, since the purpose of these experiments was to determine the response of SN cells during AD. On the basis of determinations made between seizures, we found no difference between the baseline firing rates of nigral units in kindled and naive rats (Table 2).

Table 2. Firing rates of nigral neurons in naive and kindled rats between seizures

Animal	SN dopamine	SN pars reticulata
Naive	10.3 ± 3.8 (9)	21.2 ± 3.9 (22)
Kindled	7.7 ± 1.3 (17)	17.9 ± 2.6 (32)

The numbers refer to the mean ± SEM of the firing rate (spikes/sec) of SN neurons, calculated in the 50 sec prior to initiating an AD. The values in parentheses refer to the number of cells examined. The difference in the number of cells reported in Tables 1 and 2 reflects the fact that only 65% of all recorded cells were held through the entire course of an AD. The firing rate of SN dopamine neurons reported here is faster than that typically observed (e.g., Grace and Bunney, 1984; Waszczak et al., 1980). This fast baseline firing rate may be the consequence of repeated ADs in the paralyzed state. The firing rate of SN dopamine neurons in naive and kindled rats that had not experienced AD was 4.8 ± 0.8 ($n = 5$) and 7.3 ± 1.4 ($n = 12$), respectively. There was no difference between naive and kindled cells in firing rates of nigral neurons (Student's *t* test).

Table 3. Effect of nigral lesions on afterdischarge duration (ADD) in amygdala of naive and kindled animals

Naive		Kindled	
Control	Nigral lesion	Control	Nigral lesion
9 ± 2 (10)	10 ± 1 (9)	89 ± 5 (10)	26 ± 10* (10)

The numbers refer to the mean ± SEM of ADD (in seconds). The numbers in parentheses refer to the number of animals in each group. The nigral lesions were produced with the neurotoxin NMDA, and were verified histologically. The data on kindled animals were reported by McNamara et al. (1984).
* $p < 0.001$; Student's *t* test, 2-tailed.

Administration of trains of pulses at current intensities insufficient to evoke AD produced no statistically significant change in the firing rate or pattern of SN neurons during the 10 sec following the stimulation (paired *t* test comparison of prestimulus firing rate to firing rate in the 10 sec following stimulation: 7 SN dopamine cells, 7 SNPR cells). Similarly, administration of single pulses to the amygdala did not produce a change in rate or pattern of cells in the 10 sec following the stimulation (3 SNPR cells through 10 pulses each).

Lesion experiments

Microinjection of 30 nmol of NMDA into the SN produced lesions that encompassed as much as 95% of the total volume of the SN (range, 25–95%) (Fig. 6). The behavioral manifestations of these lesions were the same as previously reported (McNamara et al., 1984). Lesions of the SN in naive animals did not suppress ADD (Table 3) or elevate ADT. ADTs in control and lesioned animals were 280 ± 33 ($n = 10$) and 333 ± 33 ($n = 9$) μA, respectively ($p > 0.05$). Furthermore, there was no statistically significant correlation between the degree of nigral destruction and the ADD or ADT based on linear-regression analyses. Thus, in contrast to the effect of SN lesions in kindled rats, the SN lesions in naive rats did not reduce ADD (Table 3).

Discussion

The 2 principal findings of this study were that (1) the majority of neurons recorded in the SN of kindled, but not naive, rats exhibited a striking change in their firing pattern during electrical seizures elicited by stimulation of amygdala, and (2) lesions of SN in naive animals, unlike kindled animals, did not suppress duration of AD in the amygdala.

Activation of SN neurons during AD: The burst-firing phenomenon

Seizures evoked by stimulation of the amygdala in kindled rats produced a dramatic change in the firing pattern of both SN dopamine and SNPR cells. The firing pattern of SN neurons of kindled rats during AD consisted of the cells firing in bursts of action potentials, with the bursts exhibiting a clear temporal relationship to specific components of the AD in EEG recordings from caudate or amygdala.

Burst-firing of dopamine cells in the absence of seizures has been previously reported (Grace and Bunney, 1983, 1984). The burst-firing of SN dopamine neurons during seizures shares some of the characteristics of this previously reported phenomenon in that the action-potential amplitude diminished during the burst and there was broadening of the action-potential waveform (data not shown). However, the spike frequency of the dopamine cells in the seizure-related bursts was much higher than the spike frequency of the cells in bursts not related to seizures (Grace and Bunney, 1984). Burst-firing of SNPR cells in the absence of seizures has not been extensively studied. However, Kaniff et al. (1983) have reported the burst-firing of
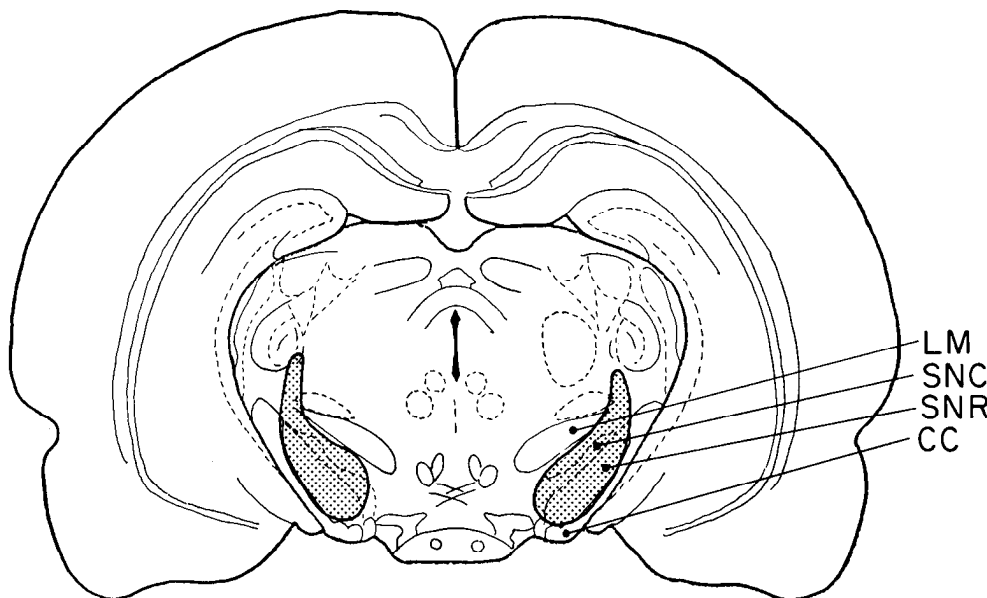
Figure 6. Reconstruction of NMDA-induced lesion. *Stippled area* represents the extent of the lesion. Figure is of a coronal section of a typical lesion. In this animal, 85% of the total SN volume was determined to be destroyed. *LM,* Medical lemniscus; *SNC,* substantia nigra pars compacta; *SNR,* substantia nigra pars reticulata; *CC,* crus cerebri.

SN neurons during penicillin-induced interictal spikes. These cells were histologically localized to the SN pars reticulata but their waveforms and firing rates were not given.

The temporal relationship between bursts of action potentials in SN neurons and AD recorded in amygdala or caudate indicates that the burst-firing of SN neurons is likely dependent upon synaptic input from structures extrinsic to SN. The presence of AD in the striatum, together with the powerful influence of striatum on nigral excitability (Dray et al., 1976), suggests that the striatum is one extrinsic structure controlling nigral bursting during seizures. However, delineation of the structures actually responsible for controlling nigral bursting during seizures will require simultaneous unit or field recordings in multiple structures, together with interventional techniques such as lesions and microinjections.

The present results suggest that nigral output is dramatically increased during kindled seizures. The switch of nigral cells into the burst-firing mode supports the idea of enhanced synaptic output from SN neurons during seizures, since firing in burst patterns has been shown to result in a 1.5–2-fold increase in postsynaptic efficacy over equally spaced spikes of the same average frequency in crustacean motor neurons (Gillary and Kennedy, 1969). Moreover, there must be at least some degree of synchronization of neurons firing in the burst pattern, since most neurons firing in bursts did so during the polyspike complex of the EEG waveform during the AD. The synchronized bursting of populations of nigral neurons almost certainly enables the SN to exert a powerful influence on its targets during seizures.

SN activation: Role in propagation of kindled seizures

Metabolic, electroencephalographic, and behavioral indices of seizure propagation demonstrate a more widespread propagation of seizure activity in kindled as compared to naive rats (for a review, see McNamara et al., 1985). The increased activation of SN neurons during AD in kindled animals indicates that the SN is one site of enhanced seizure propagation. The question of whether any of the behavioral aspects of kindled seizures can be directly ascribed to nigral activation, however, will require additional study.

The dramatic change in firing pattern of nigral neurons during AD in kindled animals leads us to hypothesize that the mechanism by which the SN facilitates seizure propagation involves

synchronous burst-firing whereby the SN transmits seizure activity from rostral sites of origin to target structures. This hypothesis finds support in the results of electrophysiologic and lesion experiments. Seizures in kindled animals are associated with burst-firing of SN neurons and are suppressed by destruction of SN. In contrast to seizures in kindled animals, the electrical seizures in naive animals are not associated with nigral burst-firing and are not suppressed by nigral destruction. Therefore, a parallel emerges between nigral neuronal activation during seizures and the presence of a seizure-facilitatory action of SN.

Findings of other investigators indicate a parallel between nigral activation metabolically and a seizure-facilitatory action of SN. Engel et al. (1978) found that the SN exhibits increased 2-deoxyglucose uptake following AD in seizures elicited in kindled, but not naive, animals, indicating that nigral unit activation parallels metabolic activation in the kindling model. Increased 2-deoxyglucose uptake has also been found in the substantia nigra in association with seizures induced by the chemoconvulsants pentylenetetrazol and bicuculline (Ben-Ari et al., 1981). Interestingly, the SN has been found to exhibit a facilitatory action in both of these chemoconvulsant models, as well as in the kindling model.

The present results are consistent with the idea that burst-firing contributes to the prolongation and enhanced spread of AD. However, the results do not exclude the possibility that the tonic activity of SNPR neurons is crucial to the seizure-facilitatory mechanism. Indeed, the seizure facilitation by the nigra may involve both tonic activity and synchronous burst-firing. Recent studies have demonstrated that the conventional anticonvulsants, phenytoin and carbamazepine, suppress high-frequency firing in a number of neuronal preparations (Macdonald et al., 1985), yet do not affect tonic activity of nigral neurons after systemic administration (Waszczak et al., 1985). To test the proposed pivotal role of SN burst-firing in seizure propagation, we are examining the effects of nigral application of these drugs, both on behavioral seizures and nigral burst-firing.

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