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Effects of Nigro-Striatal 6-OHDA Lesions on Turning Elicited by Cortical Spreading Depression

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HUSTON, J. P., L. JAKOBARTL, G. PAPADOPOULOS AND B. SIEGFRIED. *Effects of nigro-striatal 6-OHDA lesions on turning elicited by cortical spreading depression.* PHARMAC. BIOCHEM. BEHAV. 9(6) 837–843, 1978.—Rats received either unilateral 6-OHDA injections into the substantia nigra, causing ipsilateral depletions of striatal dopamine (94%) and norepinephrine (51%), or bilateral injections of same. In bilaterally 6-OHDA lesioned rats amphetamine led to circling in a preferred direction, and CSD applied to the cortex ipsilateral to that direction induced more turning than when applied to the contralateral cortex. The striatum of the hemisphere ipsilateral to the side of amphetamine-induced circling also showed a higher decrease in both dopamine and norepinephrine levels. Denervation supersensitivity in the striatum could account for the intensified circling induced from the cortex ipsilateral to the more severely depleted striatum. Measurement of DC slow potential changes in the neocortex and caudate nucleus revealed that after bilateral intranigral 6-OHDA lesions (a) an unusually large number of waves of cortical SD were transmitted to the striatum, and (b) contralateral turning was elicited also by waves of neocortical SD that did not enter the striatum.

Cortical spreading depression Turning 6-OHDA Substantia nigra Neocortex Caudate nucleus Catecholamines

WE RECENTLY found evidence for a lateralization of cortical spreading depression—induced eating after unilateral 6-OHDA injection into the substantia nigra [17]. Specifically, cortical spreading depression (CSD)—induced feeding behavior was attenuated from the cortical hemisphere ipsilateral to the 6-OHDA treated substantia nigra. Since this paradigm rules out possible motor artifacts to account for the feeding decrement, the result, for one, supports the possibility of a significant role for catecholamines in CSD-induced feeding, and secondly, demonstrates a functional interaction between the substantia nigra or nigro-striatal system and the neocortex.

The present study was conducted to further explore the possibility of nigro-neocortical interaction. Cortical spreading depression elicits contralateral turning whenever the wave of SD is transmitted from the neocortex to the striatum [1, 9, 22], which normally occurs infrequently in the Sprague-Dawley strain used in the present study (12.5% of trials, in 4.3% of SD waves [9]), but can occur with higher incidence in other rat strains [6, 7, 14, 19]). In summary, the present study investigated (a) CSD-induced turning after unilateral intranigral injection of 6-OHDA; (b) CSD- and amphetamine-induced turning after bilateral intranigral injection of 6-OHDA; and (c) incidence of transmission of cortical waves of SD into the striatum after 6-OHDA injection into the substantia nigra.

GENERAL METHOD

Animals

Forty male albino Sprague-Dawley rats of the SIV 50 strain (Tierspital Zürich) with a preoperative weight of 270–330 g were used. The animals were housed individually under a 12 hr light/12 hr dark schedule with free access to food (Nafag No. 890, Switzerland) and water. They were always tested during the light period.

Surgery

Surgery was performed under pentobarbital anesthesia (50–60 mg/kg). Each animal was implanted with four 22 ga (0.71 mm o.d., 0.41 mm i.d., 16 mm long) stainless steel cannulae, equipped with stainless steel plugs. One pair of cannulae was implanted bilaterally 1.0 mm above the rostral part of the substantia nigra using the following coordinates according to the atlas of Hurt *et al.* [8]: 1.8–2.0 mm lateral to the superior sagittal sinus, 3.2–3.7 mm anterior and 3.3 mm dorsal to the interaural line. The other pair was bilaterally implanted into the neocortex with the coordinates referenced to bregma and the surface of the skull: 0.5 mm posterior, 2.5 mm lateral, 1.0 mm ventral. The cannulae were fixed in place by dental acrylic.

Unilateral 6-Hydroxydopamine Lesions

6-Hydroxydopamine (6-OHDA) hydrochloride (Fluka Co., Switzerland) was dissolved in a cold solution of 0.1% ascorbic acid (w/v) in isotonic saline. The 6-OHDA solution was prepared shortly before injection and kept refrigerated until the time of injection. Either 4 μl of a solution containing 2 μg 6-OHDA per μl, or 3 μl of a solution containing 16 μg 6-OHDA per μl was injected unilaterally or bilaterally into the substantia nigra at a rate of 0.5–1.0 μl/min through a 28 ga (0.36 mm o.d., 0.15 mm i.d.) injection needle. The injection needle protruded from the tip of the guide cannula by 1 mm. The lesioning procedure was performed under mild pentobarbital (30–40 mg/kg) anesthesia.

Cortical Spreading Depression

Cortical spreading depression (CSD) was induced by injecting 0.2 to 0.8 μl of a 25% (w/v) KCl solution. The amount of KCl injected into a given hemisphere was increased by 0.2 μl every trial. This procedure, based on earlier electrophysiological work, guaranteed that at least one CSD-wave was elicited per trial.

Turnometer

Turning speed and direction were registered by a DC micromotor to which an animal was connected by a guitar string (G). The voltage produced by the DC motor was registered by a low-pass RC filter. The number of turns was registered by a photocell, which was interrupted by a metal pointer mounted at the axis of the DC micromotor.

Biochemical Analysis

In a sample of 6 unilaterally 6-OHDA lesioned animals (4 rats lesioned with 8 μg 6-OHDA and 2 rats with 48 μg 6-OHDA) striatal catecholamine levels were determined 14 days after the lesion with the enzymatic-isotopic method described by Palkovits *et al.* [13]. Amine concentrations were based on protein content of the tissue, determined according to Lowry *et al.* [12].

Catecholamine levels of the caudate-putamen area ipsi- and contralateral to the lesioned side were determined separately from 4 mm dia. cylinders punched out from 1.5 mm thick transverse slices that were cut about from level A 8920–A 5780 according to König and Klippel [11] coordinates [15]. In addition, measurements were made in 4 rats with bilateral nigral lesions. All rats were injected with 8 μg/4 μl 6-OHDA and exhibited amphetamine-induced circling.

Statistics

The results were treated with two-tailed *t*-tests for either related or independent samples. All average values in the text are accompanied by standard error of the mean (SEM) values.

EXPERIMENT 1. EFFECTS OF UNILATERAL NIGRAL 6-OHDA LESION ON CSD-INDUCED TURNING

METHOD

After recovery from the surgical procedure (3–5 days) the animals were unilaterally lesioned by 6-OHDA injections into the substantia nigra. Testing began after spontaneous ipsi- or contralateral circling caused by the lesion had stopped. A testing trial consisted of taking the animal out of its home cage (26×43×15 cm high), injecting KCl solution into the neocortex (experimental trials) or handling the rat as during CSD trials but without injecting it (control trials), and putting it back into its home cage. The home cage was placed into an observation box (66×118×68 cm high). The animal was then observed for 20 min, during which the direction of turning and the number of turns were recorded. The arbitrary criterion for a positive circling trial was at least two turns in the same direction occurring within 40 sec. Each animal was administered four experimental and four control trials per hemisphere, receiving one KCl and one control trial per day. The injection site and sequence of trials (experimental, control) were changed daily. Half the animals were injected first on the lesioned, and half on the nonlesioned side. After termination of the KCl tests each animal was intraperitoneally injected with 2 mg/kg amphetamine (amphetamine sulfate dissolved in isotonic saline). Circling behavior was measured for 75 min with the turnometer described above.

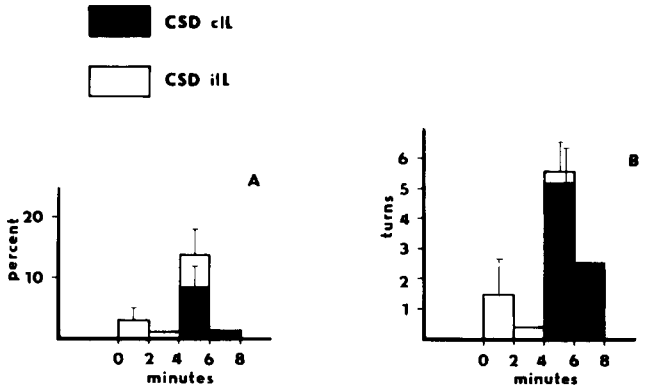

FIG. 1. (A) Mean incidence (with SEM) of CSD-induced contralateral turning from the hemispheres ipsilateral (CSD il L) and contralateral (CSD cl L) to the unilateral nigral 6-OHDA lesion in 18 animals. The incidence is expressed in percentage of all KCl injection trials per 2-min intervals during a 20-min testing period. (B) Mean number of contralateral turns induced by CSD from the hemisphere ipsilateral (CSD il L, 7 rats) and contralateral (CSD cl L, 5 rats) to the lesioned side. The values, expressed in 2-min intervals during a 20-min testing period, were calculated from all circling sessions.

RESULTS

Only those animals which showed a clearcut ipsilateral circling response after amphetamine injection were used for data analysis. Eighteen out of 28 unilaterally lesioned rats (8 out of 16 rats injected with 8 μg and 10 out of 12 rats injected with 48 μg 6-OHDA) turned ipsilaterally to the lesioned hemisphere. Ten rats which did not exhibit amphetamine-induced circling were discarded. In two of these rats CSD induced contralateral turning from the side ipsilateral to the lesion in 3 cases.

KCl tests were carried out 2 to 14 days after the 6-OHDA lesion. Of the 18 animals tested 50% showed contralateral circling during at least one of the CSD trials. The mean incidence of contralateral turning, expressed in percentages, calculated from KCl injections per animal, from the lesioned (15.3 ± 5.5%, SEM) or intact (9.7 ± 4.2%) hemisphere was not significantly different. The mean number of contralateral turns induced per KCl injection (calculated from those in which the elicited circling satisfied the criterion) was similar

for both hemispheres (lesioned hemisphere: 6.0 ± 0.9 turns; intact hemisphere: 5.9 ± 1.6 turns).

Figure 1 shows the mean incidence in percent (A) and the mean number of CSD-induced contralateral turns (B) divided into successive 2 min postinjection intervals. The highest incidence and peak frequency of circling occurred in the 4–6 min postinjection interval. Note, that turning in the 0–2 min interval was elicited only by CSD administered in the hemisphere ipsilateral to the lesioned side.

Control trials never resulted in contralateral turning.

Biochemical Analysis

The sample of 6 rats that was used for biochemical analysis revealed a significant depletion of striatal dopamine (94.1 ± 2.8%) and norepinephrine (51.6 ± 10.1%) on the side ipsilateral as compared to that contralateral to the lesion (dopamine: $p<0.001$; norepinephrine: $p<0.02$). The depletion of striatal catecholamines was not higher for those rats with high dosage (48 μg) 6-OHDA lesions.

EXPERIMENT 2. INFLUENCE OF BILATERAL INTRANIGRAL 6-OHDA ON CSD-INDUCED TURNING

METHOD

After bilateral lesioning of 11 of the 12 implanted rats (9 rats: 8 μg/4 μl; 2 rats: 48 μg/3 μl), extra palatable food (sugared condensed milk together with sweet cookies) was offered in addition to the normal rat chow on Postlesion Day 3. Those animals that did not maintain their body weight on this food were fed intragastrically twice a day with 10 ml Aminosol-Glucose (Hausmann Co., Switzerland) until they kept their body weight on the palatable food.

When the animals' consummatory behavior had recovered sufficiently to maintain their body weight on rat chow and water, they were tested according to the procedure described in Experiment 1. After receiving a total of 4 KCl and 4 control trials per hemisphere, they were injected with 2 mg/kg amphetamine IP, and tested for circling in a turnometer. On the basis of the results of this amphetamine test, the rats were divided into a group that showed circling in one direction (criterion: at least 4 turns/min during 30–45 min after amphetamine), and into another group showing no circling behavior.

RESULTS

At the beginning of the experiment, between Postlesion Days 10–22, spontaneous circling was observed in only one of the rats. Injection of amphetamine elicited turning behavior in one preferred direction in 10 of the rats, nine of which were used for data analysis. These nine animals had not shown spontaneous circling and were all lesioned with 8 μg 6-OHDA. There was no significant difference in the mean incidence of contralateral turning, elicited from the left (79.5 ± 8.3%) vs right (68.2 ± 6.6%) hemisphere. However, the mean incidence of turning induced by KCl injections into the cortex ipsilateral to the direction of amphetamine-induced turning (CSD il A) was significantly higher compared to that of turning induced by KCl injections into the cortex contralateral to the direction of amphetamine-induced turning (CSD cl A). (The total percentages were obtained by calculating for each animal a percentage value from the 4 KCl trials applied per left and right or CSD il A and CSD cl A hemisphere and by subsequent averaging of the individual percentage values.) Moreover, the mean number of turns, calculated from positive circling trials per animal over a 20 min testing period, was higher for the CSD il A group (see Table 1).

Figures 2 and 3 illustrate the mean incidence in percent and mean number of CSD-induced contralateral turns over 2 min intervals. Significantly higher mean incidence and mean number of contralateral turns, calculated per interval, were obtained by cortical KCl injections into the hemisphere ipsilateral to the direction of amphetamine-induced turning (see Table 1). Turning occurred most likely and with highest frequency within the first 6 min after injection of KCl in both groups. The CSD-induced contralateral turning intensity of the CSD cl A group (6.8 ± 0.4 turns/min) was significantly lower compared to that of the CSD il A group (12.0 ± 1.5 turns/min, $p<0.05$). (The turning intensity, expressed in turns/min, was calculated individually for each positive circling session per animal by dividing the number of turns per session by the interval from the first (range: 15 sec–6 min) to the last (range: 4 min–20 min) turn, and by subsequent averaging of the individual values.)

Control trials never resulted in contralateral turning; and none of the KCl injections resulted in ipsilateral circling.

Biochemical Analysis

In four of the bilaterally lesioned (8 μg 6-OHDA) rats which showed circling in the amphetamine test, catecholamine levels in the caudate-putamen area were determined. Both, dopamine and norepinephrine levels were decreased significantly more on the side ipsilateral to the

TABLE 1

CSD-INDUCED CONTRALATERAL TURNING IN RATS WITH BILATERAL 6-OHDA LESIONS OF SUBSTANTIA NIGRA

Stimulus application	Incidence of contralateral turning in percentage of		Contralateral turns calculated from	
	KCl injections per animal over 20 min	all KCl injection trials per 2 min intervals over 20 min	circling sessions per animal over 20 min	all circling sessions per 2 min intervals over 20 min
CSD il A	88.9 ± 6.0†	32.2 ± 6.5‡	5.3 ± 16.5*	5.4 ± 1.1‡
CSD cl A	61.1 ± 9.4	14.7 ± 4.6	13.3 ± 6.1	1.2 ± 0.5

*$p<0.05$.
†$p<0.01$.
‡$p<0.001$.

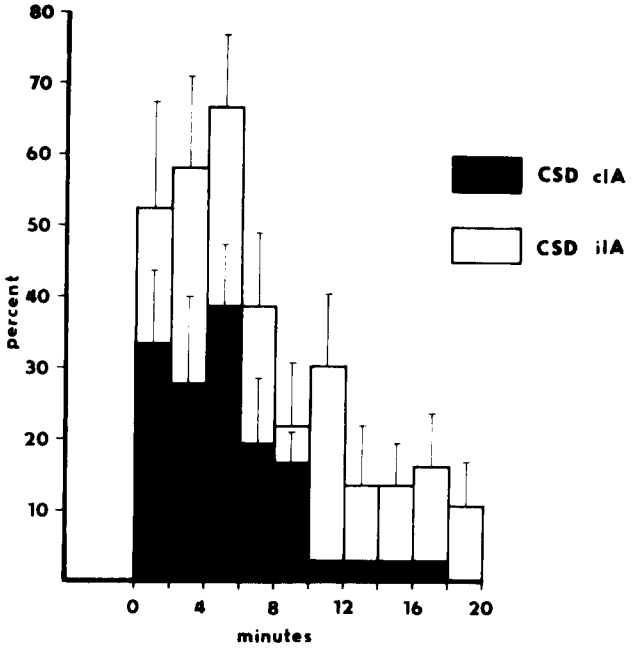

FIG. 2. Mean incidence of CSD-induced contralateral turning, calculated from all KCl injection trials, from the hemispheres contralateral (CSD cl A) or ipsilateral (CSD il A) to the side toward which turning was induced by amphetamine. Results are divided into 2-min intervals during a 20-min testing period for 9 bilaterally 6-OHDA lesioned rats (with SEM).

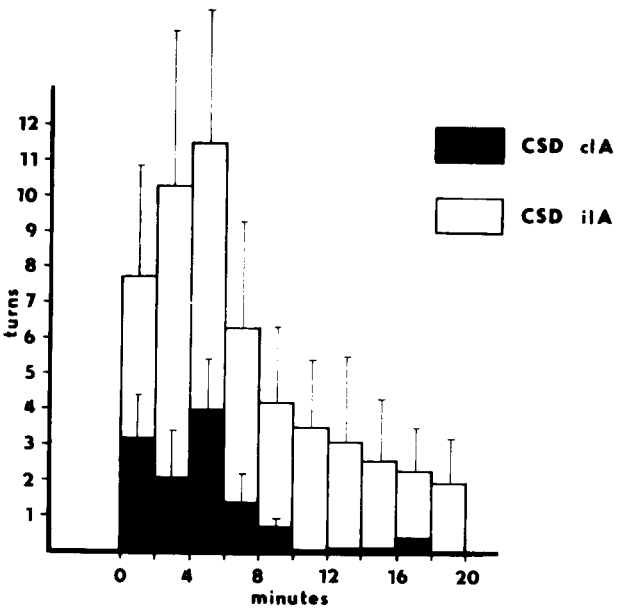

FIG. 3. Mean number of contralateral turns (calculated from all circling sessions) induced by CSD from the hemispheres contralateral (CSD cl A) and ipsilateral (CSD il A) to the side toward which turning was induced by amphetamine. Results are presented in 2-min intervals during a 20-min testing period (with SEM) for 9 rats bilaterally lesioned with 6-OHDA.

TABLE 2

DOPAMINE AND NOREPINEHPRINE LEVELS IN CAUDATE-PUTAMEN AREA IN HEMISPHERES IPSI- AND CONTRALATERAL TO THE DIRECTION OF AMPHETAMINE-INDUCED TURNING. VALUES ARE GIVEN AS NG AMINE/PROTEIN, WITH STANDARD ERROR OF MEANS

	Hemisphere ipsilateral to direction of amphetamine-induced turning	Hemisphere contralateral to direction of amphetamine-induced turning
Dopamine (ng/mg protein)	1.45 ± 0.45 (n=4)	15.9 ± 4.6 (n=4)
Norepinephrine (ng/mg protein)	0.76 ± 0.27 (n=4)	1.89 ± 0.3 (n=4)

amphetamine-induced turning direction ($p<0.05$). Table 2 presents the values in ng amine/mg protein. The absolute dopamine and norepinephrine values of the lesioned striatum in unilateral 6-OHDA lesioned rats (n=6) were 5.3 ± 2.4 and 1.8 ± 0.3 ng amine/mg protein, respectively.

EXPERIMENT 3. TURNING AND CORTICO-CAUDATE TRANSMISSION OF CSD AFTER INTRANIGRAL 6-OHDA

METHOD

Animals

The animals were 6 rats with bilateral 6-OHDA lesions in the substantia nigra. All had exhibited amphetamine-induced turning exclusively to one side in Experiment 2.

Surgery

Surgery was performed under light pentobarbital anesthesia (40 mg/kg). The assembly, including the cortical and nigral injection cannulae, was carefully removed. DC recording calomel electrodes [16] (tip dia. 100–200 μm) were implanted unilaterally into the caudate nucleus ipsilateral to the amphetamine-induced turning direction (0.0; 4.5; 4.0 mm). The coordinates of the caudate electrode were referenced to the bregma (anterior-posterior/lateral/ventral from the dura) with lambda and bregma on a horizontal plane. DC recording electrodes were also implanted bilaterally into the neocortex (0.5 mm ventral from the dura). The positions of the cortical electrodes in anterior-posterior and lateral direction varied, depending on the condition of the damaged skull. One cortical KCl-injection cannula (16 mm long, 22 ga) was implanted

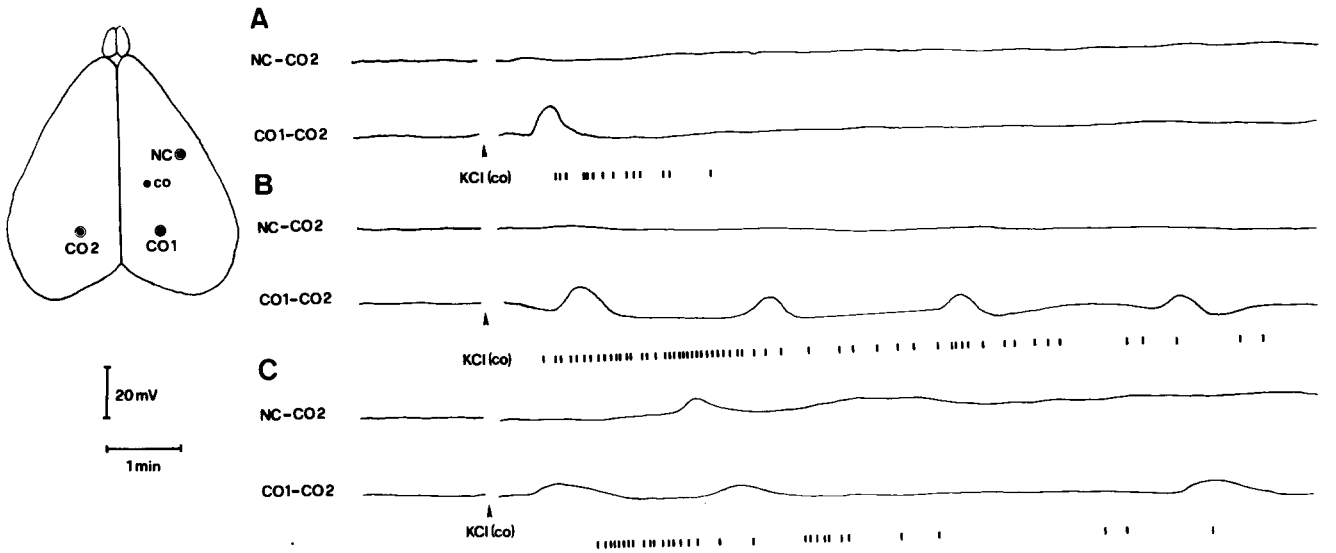

FIG. 4. Samples of Cortical (CO1–CO2) and caudate (NC–CO2) DC slow potential recordings after cortical (co) KCl injection. Electrode CO2 served as the common reference electrode. Cortical KCl injection is indicated by arrow, a full turn by dashes. Examples A and B were taken from the same animal. (A) circling accompanying a single cortical wave. (B) circling accompanying multiple cortical waves. (C) circling accompanying multiple cortical and one cortico-caudate transmitted striatal spreading depression wave. Note the short latency of the striatal spreading depression wave (2.9 min).

ipsilaterally to the caudate electrode (ventral: 0.5 mm from the dura). The preparation is depicted in Fig. 4.

Apparatus

The experiments were carried out in an electrically shielded sound-proof observation chamber (60×60×75 cm high), into which the rat's home cage was placed. Rat chow (cubes) was liberally scattered over the floor, and water was available from a spout situated 12 cm above the floor. DC potential changes were registered by DC coupled differential amplifiers (Tektronix, Type 26A2), and recorded with a polygraph.

Testing Procedure

Each animal was tested once a day, six days in succession. One test consisted of a microinjection of 25% KCl (w/v), which was repeated whenever no wave of CSD was generated (volume: 0.5–3.5 μl). Contralateral circling was recorded on the DC records with a hand-operated event-recorder. After 10 min of DC baseline recording, the KCl solution was injected, and DC slow potential changes were recorded from the neocortex and caudate nucleus. The animal's behavior was observed for 20 min.

Histology

After the experiments the brains were removed, fixed in Formalin, sliced, stained, and examined for correct placement of the caudate recording electrode.

RESULTS

A total of 36 tests were carried out. However, due to the age of the preparation, only 23 tests resulted in CSD with recordings unambiguous enough to warrant inclusion for data analysis.

Contralateral Circling

Cortical application of KCl induced circling in all 23 testing trials. Contralateral circling was induced by either cortical or cortical plus striatal SD waves (due to cortical waves propagating to the caudate nucleus). In 14 trials (5 rats) the cortical waves propagated to the caudate nucleus (transmis-

TABLE 3

LATENCIES OF CSD WAVES AND CONTRALATERAL TURNS IN RATS WITH BILATERAL 6-OHDA LESIONS OF SUBSTANTIA NIGRA

Trials	Animals (n)	Onset of first cortical wave (s)	Onset of first contralateral turn (s)	Total turns	
				single wave	multiple waves
Transmission trials	5	42.2 ± 4.5 (12–127)	65.1 ± 5.7 (12–96)	26.8 ± 5.4 (4–103)	
Nontransmission trials	3	54.4 ± 6.0 (20–152)	54.9 ± 11.7 (20–88)	26.2 ± 3.4 (4–60, n=6 tests)	37.3 ± 10.1 (22–66, n=3 tests)

Numbers in parentheses give range.

sion trials), whereas in 9 trials (3 rats) the waves did not propagate to the striatum (nontransmission trials). The onset times of the first CSD wave, the first contralateral turn, as well as the number of contralateral turns are given in Table 3. Examples of cortical KCl-induced short latency contralateral circling are illustrated in Fig. 4 for nontransmission and transmission trials.

Cortico-Caudate Transmission

Thirty-nine percent of 57 cortical waves, elicited in 14 out of 23 tests in 5 of the 6 rats, were transmitted to the caudate nucleus. The mean onset of striatal SD waves was 4.2 ± 0.4 min (range 1.0–7.4 min). In 63.6% of cases a striatal SD wave was recorded within 4 min after the cortical KCl injection.

DISCUSSION

The rats given unilateral intranigral 6-OHDA injection were comparable to normal animals in terms of the incidence and onset of CSD-induced contralateral turning, as well as the number of turns per injection [9,18]. These animals, however, showed a trend (though not significant) toward a higher incidence of contralateral turning induced from the cortex on the side of the lesioned compared to the nonlesioned hemisphere. In a few cases (2.8% of KCl injections, which, however amount to 17% of the cases in which turning occurred, the unilaterally lesioned rats showed contralateral turning very shortly (0–2 min) after application of KCl to the cortex on the side of the lesioned substantia nigra. This was never observed in the nonlesioned hemisphere, nor in normal animals [9,18]. This short-latency effect was much more pronounced in the bilaterally 6-OHDA lesioned rats, in whom contralateral turning occurred within 2 min after KCl application in 54.5% of trials from the cortex ipsilateral and 33.3% of trials from the cortex contralateral to the direction of amphetamine-induced turning. The bilaterally lesioned rats also exhibited a high incidence of CSD-induced contralateral turning compared to normals and unilaterally 6-OHDA treated animals, with the incidence significantly higher from the hemisphere ipsilateral to the direction of amphetamine-induced turning. In these animals the mean number of turns per trial as well as the rate of CSD-induced turning were also higher from the hemisphere ipsilateral vs contralateral to the side of amphetamine-induced turning.

The elicitation of ipsilateral turning by amphetamine can be taken as an indirect measure of the effectiveness of unilateral 6-OHDA nigrectomy in terms of the depletion of telencephalic dopamine (DA) levels [21]. Therefore, the elicitation of turning by amphetamine in the bilaterally 6-OHDA treated rats was taken as an indicator of an asymmetry in damage; i.e., the hemisphere ipsilateral to the direction of amphetamine-induced turning was assumed to have suffered more severe DA depletion.

This assumption was confirmed by biochemical determination of dopamine in the caudate-putamen area, which showed significantly more depletion of dopamine in the hemisphere ipsilateral to the direction of amphetamine-induced turning. Thus, in summary, in bilaterally lesioned rats, the imbalance in striatal dopamine level was accompanied by a quantitative and qualitative hemispheric asymmetry in spreading depression-induced turning; i.e., in the more severely lesioned hemisphere CSD resulted in a higher incidence of turning and higher number of turns per trial, as well as in a higher incidence of short-latency (<2 min) turning.

The results of Experiment 3 suggest that the short latency CSD-induced contralateral turning in bilaterally (and probably also in unilaterally) lesioned rats was due to a slow potential change that was restricted to the neocortex, since in 22 out of 23 trials, and especially in the 9 trials in which the wave of SD did not enter the striatum, contralateral circling was induced with a very short latency (<1 min) which coincided with the presence of a wave of SD in the neocortex. This result is rather surprising, considering that in normal animals turning only occurs when the wave of SD enters the striatum [9,22]. Since a well documented change after 6-OH-dopamine lesions of the substantia nigra is "denervation supersensitivity" of the striatal dopamine receptors [20], it is tempting to speculate that turning without striatal invasion of the SD wave could be due to striatal "supersensitivity" to cortical influences during the cortical SD. However, it is not easy to establish a connection between the known dopamine receptor supersensitivity and "supersensitivity" of striatum to cortical influences, although such influences can logically be assumed on the basis of known corticostriatal connections. In a functional way such influences are indicated by the results of Keller *et al.* [10] who found increased dopamine turnover after cortical SD. However these results cannot easily be generalized to a state of severe dopamine depletion in striatum, and it is difficult to judge whether an eventual increase of dopamine turnover under such circumstances should lead to a qualitatively different result (turning in the absence of striatal SD) in comparison to intact animals. On the other hand, if one assumes that turning in such cases is brought about by a neuronal influence on the striatum, leading, in some way, to activation of dopamine receptors, it is rather logical that turning would be more intense when the more severely dopamine depleted striatum (whose dopamine receptors would consequently be more supersensitive) were involved. This could also explain our finding that turning was more pronounced when cortical SD was induced ipsilaterally to the direction of amphetamine turning; i.e., to the side of more complete striatal dopamine depletion. In a more general way one could speculate that an intact dopaminergic system in the striatum in some manner counteracts cortico-caudate influences that are activated during cortical spreading depression and which are also involved in contralateral turning in the intact animal. In the DA-denervated striatum this dopaminergic action is eliminated so that cortical influences predominate and contralateral turning becomes manifest. The evidence for the existence of a direct neocortico-nigral projection [2] offers another interesting possibility for a direct influence of the cortex on structures that control turning. But a more detailed hypothesis is precluded by the lack of information about the nature and function of such connections.

In bilaterally lesioned animals the rate of transmission of waves of spreading depression from the neocortex to the caudate nucleus was much higher (39% of waves, 61% of trials) than in nonlesioned rats of the same strain (4.3% of waves in 12.5% of trials [9]). Furthermore, the latency with which the slow potential change (SPC) reached the striatum in the bilaterally lesioned rats was shorter than in normal rats. Whereas in normal rats the latency is 4–6 min [5, 7, 9], in bilaterally lesioned rats the mean latency was 3.8 min. These results could only be partially reproduced in hooded Holzman rats with unilateral 6-OH-dopamine lesions in the substantia nigra. In an unpublished study with 8 such rats

tested under pentobarbital anesthesia there was a clear cut reduction in the cortico-caudate conduction time (2.8 min). On the other hand, no difference in the rate of transmission was found between intact and lesioned hemispheres and no increase in the incidence of striatal SD (26.5% of waves, 38% of trials) as compared to results in intact rats from the same strain reported earlier (34% waves [5]). It should be noted, however, that the rate of cortico-caudate transmission was already very high compared to the strain used in the present study.

It is known that transmission of waves of SD from the neocortex to the striatum (and vice versa) is labile. For one, strain differences appear to exit in terms of incidence of transmission of SD between the striatum and neocortex [9]. Furthermore, the age of the animal plays a role [3], as does the history of nutrition of the animal: An increase in the incidence of cortico-caudate transmission is caused by early undernutrition [4]. Such an increase was also caused by injection of a pyrrolopyrimidine derivative [5]. The nature of the connection between these results and our findings remains obscure. It is clear that any explanation should take into account the fact that the findings in bilaterally lesioned animals were only partially or only weakly reproducible in unilaterally lesioned animals. This fact defies any simple explanation in terms of catecholamine (dopamine) depletion or dopamine receptor supersensitivity. Such a difference between unilaterally and bilaterally lesioned rats could be due to nutritional factors, since such factors have elsewhere [4] been shown to influence the incidence and speed of cortico-caudate transmision of SD and since the existence of a different nutritional state in bilaterally lesioned animals as compared to both unilaterally lesioned and intact animals cannot be excluded.

Another factor that should eventually be taken into account is that the time elapsed between lesion and testing was generally longer in the group of bilaterally lesioned animals and even longer in the group in which slow waves were recorded from the striatum. It is true that the best known changes after 6-OH-dopamine lesion in the substantia nigra (catecholamine depletion, dopamine receptor supersensitivity) develop quite quickly, but it is difficult to estimate the time course of possibly more subtle secondary changes, which could lead to increased transmission rate, decreased transmission time, as well as the appearance of turning without caudate invasion of the SD wave. Therefore, more work is needed in this direction in order to clarify the mechanisms underlying the above findings.

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