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A Biphasic Influence of Globus Pallidus Lesions: Spontaneous Catalepsy Followed by Anticataleptic Effect

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OSSOWSKA, K., M. ŚMIAŁOWSKA, AND S. WOLFARTH. *A biphasic influence of globus pallidus lesions: Spontaneous catalepsy followed by anticataleptic effect.* PHARMACOL BIOCHEM BEHAV **19**(2) 169–176, 1983.—The behavioural and histological effects of unilateral or bilateral lesions induced by kainic acid injections into the globus pallidus were investigated in rats. Both lesions provoked a behavioural syndrome similar to those seen in animals treated systemically with neuroleptics or opiates. Animals displayed akinesia, ptosis, catalepsy, hypothermia and muscular rigidity. Also a marked hypersensitivity to touch, and a sensory neglect to touch and pain limited to hindlegs, adipsia, aphagia and high mortality of lesioned rats were observed. These symptoms were much stronger and lasted longer (catalepsy lasted over 15 days) in bilaterally lesioned animals. Subcutaneous injections of apomorphine in bilaterally lesioned rats abolished akinesia and catalepsy while rigidity and ptosis were unaffected. In unilaterally lesioned rats in which the lesion-induced spontaneous catalepsy already disappeared the spiperone-induced catalepsy was suppressed while in bilaterally lesioned animals which showed still pronounced lesion-induced catalepsy the spiperone-induced catalepsy was unchanged when compared to the sham-operated rats. Our results and the literature data suggest that the lesions of the globus pallidus produce biphasic effects: spontaneous catalepsy and unchanged neuroleptic catalepsy in the first phase and suppression of the neuroleptic catalepsy in the second phase. The role of the globus pallidus as a distal link (for neostriatum and n. accumbens) in neuronal chain forming a matrix of central patterns of catalepsy, akinesia and rigidity is discussed.

Globus pallidus Kainic acid Apomorphine Spiperone catalepsy Ridigity Akinesia Aphagia

IT IS generally accepted that a degeneration of the dopamine pathways starting from the substantia nigra region constitutes the main cause of Parkinson's disease [13, 17, 19, 42]. Lesions of the substantia nigra in different animal species did not produce, however, behavioural effects which are easily comparable to those seen in the course of that illness (bradykinesia, rigidity and tremor) [14,17]. Only bradykinesia and occasionally tremor were observed in monkeys [14] and rats (see [13]) after bilateral lesions of the substantia nigra. Moreover, a recently developed technique of reinnervation of the denervated striatum by transplanting the embryonic substantia nigra tissue which replaces missing dopamine synapses compensates only partially for the behavioural deficits induced by the lesions of dopamine pathways [13].

In the course of Parkinson's disease cell degenerations are observed not only in the substantia nigra but also, particularly in a later period of the illness, in the globus pallidus (see [22]). Surprisingly, although lesions of the globus pallidus are used to alleviate symptoms of the Parkinson's disease [17,19] akinesia and catalepsy were described in animals after electrothermic lesions of the structure [45]. The participation of the globus pallidus in neuroleptic-induced catalepsy, a pharmacological model of Parkinson's disease, is also unequivocal. According to some authors an electrothermic lesions of the globus pallidus strongly suppresses the neuroleptic-induced catalepsy [6, 7, 9] while others describe the same lesion as ineffective [44]. Therefore, both pathophysiological and the pharmacological roles of the globus pallidus seem to be unclear.

Globus pallidus contains many passing fibres and neurons of different morphology [4, 29, 30, 41]. To resolve these controversies we employed, in this study, specific chemical lesions with kainic acid which destroys the neuronal bodies but leaves the passing fibres intact [32].

METHOD

Surgery and Drugs

Experiments were carried out in male Wistar rats, weighing 250–300 g just prior to surgery. In pentobarbitone (Vetbutal, Biowet, Poland, 30 mg/kg IP) anaesthesia an external, stainless-steel, guide cannula (or cannulas) (ext. diameter 0.4 mm) was introduced stereotaxically, uni- or bilaterally to the upper limit of the globus pallidus, afterwards an internal cannula (ext. diameter 0.3 mm) was inserted into the globus

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pallidus (GP), i.e., 1.8 mm below the trip of the guide cannula, at A=7.4, L=2.8, H=3.9, according to the atlas of Albe-Fessard *et al.* [1]. After that, through the internal cannula kainic acid (Sigma), or 0.2 M phosphate buffer (pH=7.4) for control sham-operated rats, was injected in a constant volume of 0.1 μl/GP. Kainic acid was dissolved in the phosphate buffer and injected unilaterally in doses of 0.1 or 0.5 μg or bilaterally in a dose of 0.3 μg/GP, using a Hamilton syringe of total volume of 1 or 2 μl. The injection lasted 1 min and the internal cannula was left inside the guide cannula until 1 min after the injection. Both cannulas were afterwards withdrawn and the skin on the skull was sutured. After surgery the rats were housed in separate wire cages (21×21×24 cm) with free access to water and food pellets.

On the 7th day and 11th day after the lesions rats were injected subcutaneously with 1.0 or 2.5 mg/kg of apomorphine (Sandoz), and subsequently on the 15th day the rats received intraperitoneally 0.2 mg/kg of spiperone (Janssen Pharmaceutica Ltd).

Behavioural Tests

Behavioural observations started immediately after the end of anaesthesia and were carried out for 0.5–1 hr. The behavioural observations and tests were repeated every day between 10 a.m. and 4 p.m. until the 15th day after the lesion. The catalepsy was scored by the method of Delini-Stula and Morpurgo [10] and sometimes, to obtain a more precise insight in the phenomenon also by a modification of the method of Costall *et al.* [8]. Briefly, the modification consisted in placing rats with their forepaws on a 9 cm high bar (Fig. 1C) and measuring the time they maintained this unnatural position according to the following point system: 0 point—0–14 sec, 1 point—15–39 sec, 2 points—40–59 sec, 3 points—60–119 sec, 4 points—120–179 sec.

Estimations of the muscle tone were based on the method used by clinicians and consisting of observations and evaluation of muscle tone by touch and of the resistance to flexions opposed by the extremities.

Estimations of the sensitivity to touch and pain were tested by touching the rat with a sharp or dull pin.

The assessment of stereotyped behaviour induced by apomorphine was carried out until 1 hr after the injection. The number of animals demonstrating stereotyped sniffing, licking or gnawing was noted.

In some experiments the core temperature of rats was measured in the esophagus with an "Ellab" termistor thermometer.

Histology and Statistics

After the end of the experiment, usually on the 15th day after the lesion, the animals were killed by an overdose of pentobarbitone, then the brains were removed, fixed in a 10% formaldehyde solution and examined histologically by means of photographs taken directly from unstained frozen brain slices. This method allowed the selection of rats in which the tip of the cannula was located within the globus pallidus. All other animals were eliminated from the experiment. Six brains were examined in more detail (3–5 days after kainic acid injections and estimations of the behavioural deficits) for histological demonstration of the extension of the lesions in the globus pallidus and other brain structures. These brains were cut on 10 μm frontal sections between the level of the anterior neostriatum and posterior mesencephalon (A=8.5–2.6 [27]) and stained for nerve cell bodies and myelinated fibres with cresyl violet and luxol fast blue.

The statistical comparison of different groups of rats was carried out with Student's *t*-test, with a two-sample Wilcoxon's or with Fisher's exact probability test.

RESULTS

Behaviour of Rats Immediately After the End of Anaesthesia

Injections of kainic acid into the globus pallidus produced initially contralateral head-to-tail rotations, rotations around the long axis of the body (barrel-like rotations), a strong enhancement of locomotor activity, intensive stereotyped sniffing and different kinds of epileptic phenomena.

The head-to-tail rotations appeared in all rats after unilateral injection of the dose of 0.5 μg (n=8) and in 2 out of 6 rats after a unilateral injection of 0.1 μg of kainic acid. In the first group the peak frequency of rotations was 22 turns/min. Barrel-like rotations appeared in only 4 out of 8 rats, only after the high dose of kainic acid. Both unilateral (0.5 μg/GP) and bilateral (0.3 μg/GP) injections of kainic acid strongly enhanced the locomotor activity of rats, induced intensive stereotyped sniffing and provoked seizure-like movements of the mouth, clonic convulsions of the forelegs and occasionally even generalized clonic-tonic convulsions. All these phenomena lasted for more than 5 hr.

Behaviour of Rats Between the 1st and the 15th Day After the Globus Pallidus Lesions

As early as on the first day after the unilateral injection of kainic acid the direction of head-to-tail rotations changed. Instead of quick contralateral rotations very slow ipsilateral rotations were observed. Rats completed one full circle during approximately 1 min. The rotary motion was frequently interrupted for few seconds by freezing behaviour insertions. These ipsilateral rotations appeared in all rats receiving 0.5 μg of kainic acid (Fig. 1) and in one out of six animals treated with 0.1 μg of kainic acid. In addition to the short episodes of freezing behaviour, long intervals of immobility were intermingled with relatively short periods of rotations. The number of rats in which rotations were observed decreased in the next few days (Fig. 4).

After bilateral injections (0.3 μg/GP) of kainic acid and also after unilateral injection of 0.5 μg of the drug, pronounced immobility was the most obvious behavioural phenomenon. Rats assumed a hunched-back posture and remained in one corner of the cage changing this position only rarely. If touched, even very gently, they reacted violently with a vehement jump and escaped. When placed gently on a table they extended the hindlegs rigidly (only one leg on the opposite side to the lesion after unilateral lesions) but still maintaining the hunched-back posture (Fig. 1). Distinct enhancement of the muscle tone was observed particularly in the hindlegs of the lesioned rats. In lesioned rats, especially after bilateral lesions also prominent ptosis, hypothermia, sensory neglect (to touch and pain limited to the skin of hindlegs), adipsia and aphagia, and a rapid decrease of body weight were observed. In unilaterally lesioned rats sensory neglect was seen predominantly on the contralateral side. Body temperature measured occasionally in some of the lesioned rats fell by 3–4°C.

Rats with strong adipsia and aphagia and decline of body weight progressively ceased to react to external stimuli and

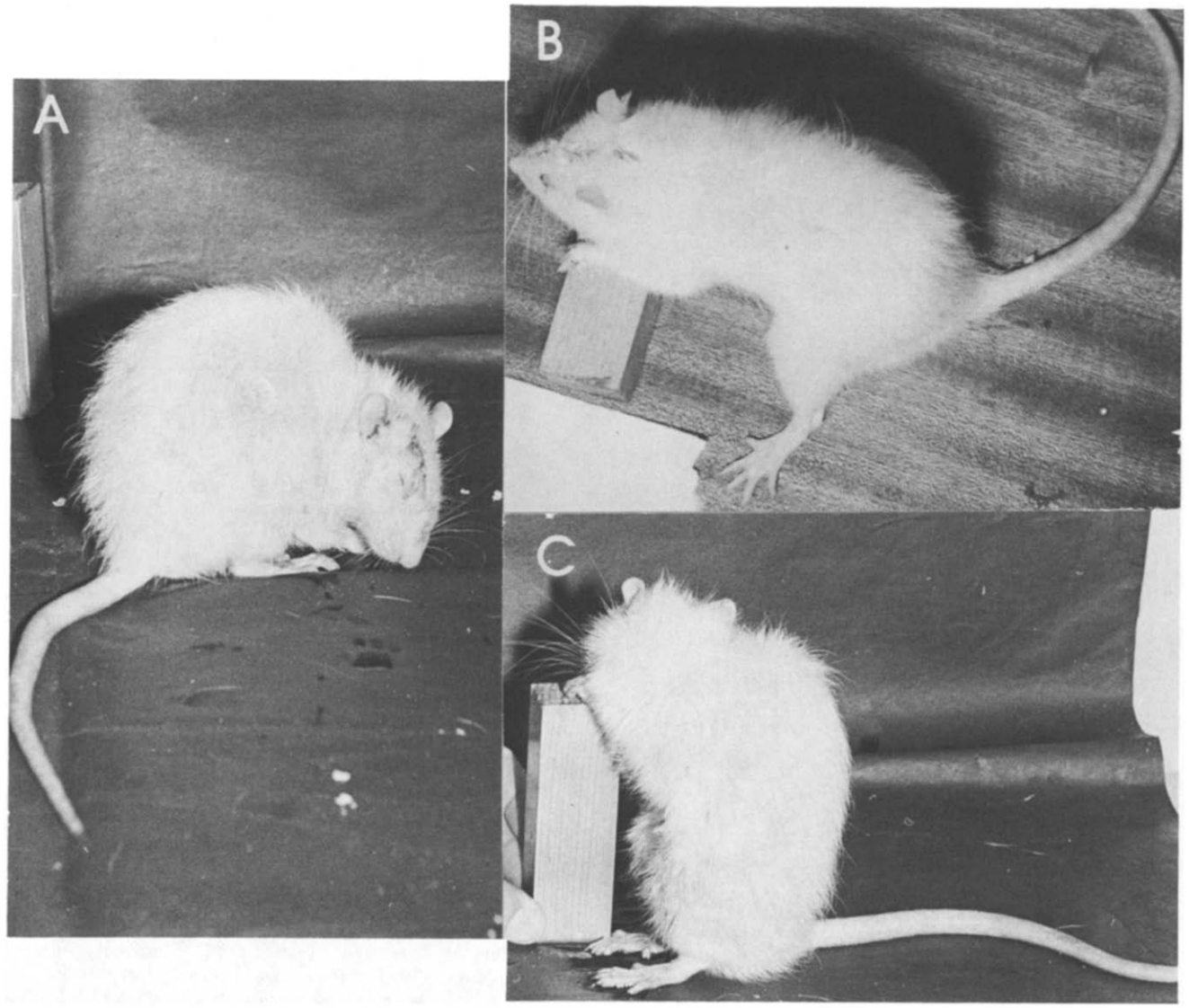

FIG. 1. The behaviour of rats 3 days after bilateral or unilateral kainic acid lesions of the globus pallidus. A—bilateral lesion (0.3 μg/0.1 μl/GP of kainic acid); note: hunched-back posture of the rat and strong ptosis; B—unilateral lesions of the right globus pallidus (GP) (0.5 μg/0.1 μl/GP), note: rigid abduction of the contralateral hindleg; C—the same lesion as in "B"; note: ipsilateral twist of the rat's head and neck and hunched-back posture during the catalepsy measurement.

died within the first week after the surgery. Because of that, about 40% of rats after unilateral injection of 0.5 μg of kainic acid and 80% of rats after bilateral treatment (0.3 μg/GP) were eliminated from the experiment (comp. [6, 7, 9, 28]).

Although the animals reacted to touch violently, when gently placed on the bar, they maintained the unnatural position (Figs. 1 and 2A, 2B) and showed a pronounced ptosis. In rats with unilateral lesion of the globus pallidus the catalepsy disappeared within the first week after the surgery (Fig. 2A) while after bilateral lesions the cataleptic reaction persisted over 15 days (Figs. 2A,B). It is interesting to note that after the first 8 days of the daily handling and tests, rats habituated themselves to the manipulation so far as to "learn" to persist in the abnormal position for some time (Fig. 2B).

The Effects of Apomorphine and Spiperone on the Behavioural Changes Induced by Globus Pallidus Lesions

Apomorphine in both 1.0 and 2.5 mg/kg SC doses injected on the 7th and 11th day after bilateral kainate lesions abolished the catalepsy (Fig. 3) and akinesia without affecting the muscular rigidity and ptosis induced by the lesions.

Apomorphine given to rats with unilateral lesions at the time when ipsilateral rotations were diminished by 50% (Fig. 4) brought back the rotational behaviour. Moreover, the rotational behaviour appeared also in some sham-operated rats, although the animals have never shown this behaviour before. The stereotyped licking induced by apomorphine was decreased or abolished in lesioned rats (Table 1), apomorphine-induced gnawing appeared only in lesioned

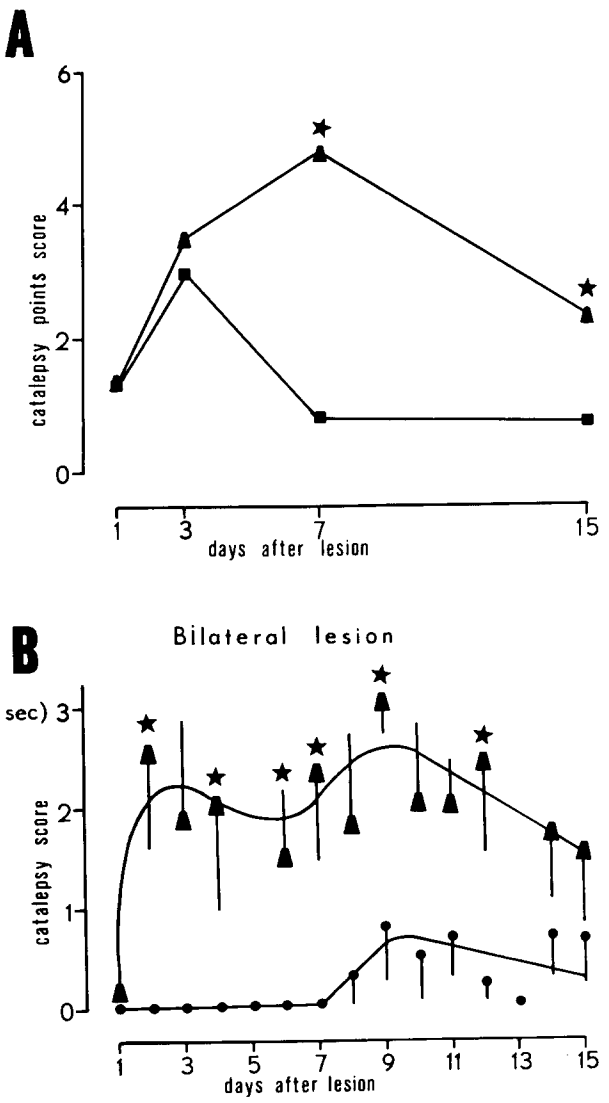

FIG. 2. Catalepsy induced by kainic acid lesions of the globus pallidus (GP). Upper part (A) of the figure presents the comparison between the effects of uni- and bilateral lesions; catalepsy was scored according to a modified 6 points scale of Delini-Stula and Morpurgo [10]; the lower part (B) shows the effects of bilateral lesions; catalepsy was scored daily using a modified method of Costall *et al.* [8] where 3 points denotes unnatural position lasting over 60 sec; filled circles—sham-operated rats (n=7), filled triangles—rats lesioned bilaterally with 0.3 μg/0.1 μl/GP of kainic acid (n=6), filled squares—rats lesioned unilaterally with 0.5 μg/0.1 μl/GP of kainic acid (n=8), asterisk—difference is significant at $p<0.05$ (Wilcoxon's two-sample test at A or Student's *t*-test at B) either between uni- and bilateral lesioned rats (A) or between lesioned and sham-operated rats (B).

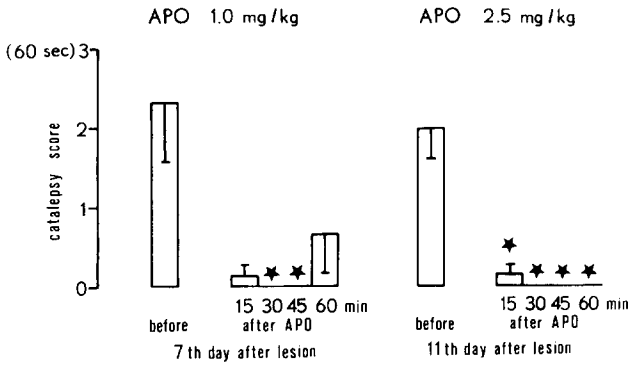

FIG. 3. The effects of subcutaneous apomorphine injection on catalepsy induced by bilateral kainic acid lesions of the globus pallidus (GP). Catalepsy was scored according to a modified method of Costall *et al.* [8]; bars represents mean±SEM, asterisk—difference to "before drug group" is significant at $p<0.05$ (Student's *t*-test).

animals, and stereotyped sniffing remained unchanged by the lesions of the globus pallidus.

Catalepsy induced by 0.2 mg/kg of spiperone injected on the 15th day after bilateral lesion was considerably stronger (according both to the scale of Delini-Stula and Morpurgo [10] and to the scale of Costall *et al.* [8]) than that scored in the lesioned rats before the injection. However, the catalepsy induced by spiperone was equally strong in bilaterally lesioned and in sham-operated rats (according to both scales). In rats with unilateral lesion of the globus pallidus spiperone-induced catalepsy was reduced when compared to sham-operated rats. The higher dose of the kainic acid (0.5 μg) provoked a stronger reduction of the spiperone catalepsy (Fig. 5).

Histology

Bilateral injections of 0.3 μg of kainic acid into the globus pallidus resulted, in all rats, in a bilateral almost total loss of nerve cell bodies within this structure and in the destruction of distant neurons. All globus pallidus neurons except those located in the ventro-medial and posterior parts of the structure were destroyed (Fig. 6). Besides, the bilateral kainate injections always induced substantial neuronal degenerations in the following nuclei of the thalamus (terminology according to the atlas of König and Klippel [27]): n. reticularis, n. paratenialis, n. medialis (pars medialis and pars lateralis), n. anterior medialis and n. lateralis (Fig. 6). In some animals nerve cell destruction were seen occasionally (Fig. 6) in further thalamic nuclei, in n. anterior ventralis, n. ventralis, n. posteromedianus, n. parafascicularis, n. lateralis (posterior part), n. reuniens and sometimes within the n. dorsalis corporis geniculati lateralis, in the reticular part of the substantia nigra, and within the n. entopeduncularis. Occasionally a narrow degeneration zone neighbouring to the globus pallidus in the caudatus-putamen and in the peripallidal region was seen.

The unilateral injection of 0.5 μg of kainic acid into the globus pallidus resulted in a similar but unilateral lesion of the injected structure (unilateral injection of 0.3 μg of kainic acid produced almost the same lesion of the globus pallidus [35]) and of n. reticularis thalami, and in bilateral lesions of n. paratenialis and n. medialis (medial and lateral parts) thalami. After the injection of 0.5 μg of kainic acid neurons also became less numerous in the n. entopeduncularis and in the narrow part of the caudatus-putamen neighbouring to the globus pallidus. Extensive loss of neurons was seen in the CA 1 field of the hippocampal formation. More detailed information on the histological examination of the effects of

TABLE 1

THE EFFECTS OF THE GLOBUS PALLIDUS LESIONS ON THE APOMORPHINE-INDUCED STEREOTYPIES

	Unilateral			Bilateral			
	solvent 0.1 μl	KA† 0.1 μg	KA 0.5 μg	solvent 0.1 μl	KA 0.3 μg	solvent 0.1 μl	KA 0.3 μg
Stereotypies	APO‡ 2.5 mg/kg			APO 2.5 mg/kg		APO 1.0 mg/kg	
Sniffing	14(14)§	6(6)	8(8)	7(7)	6(6)	7(7)	6(6)
Licking	8(14)	4(6)	0(8)*	4(7)	4(6)	7(7)	2(6)*
Gnawing	5(14)	2(6)	4(8)	0(7)	5(6)*	0(7)	4(6)*

†Kainic acid, ‡apomorphine, §the number without parentheses denotes the number of rats in which a given symptom was observed while the number in parentheses denotes the number of rats used; *Significant ($p<0.05$) to the solvent treated group according to Fisher's exact probability test.

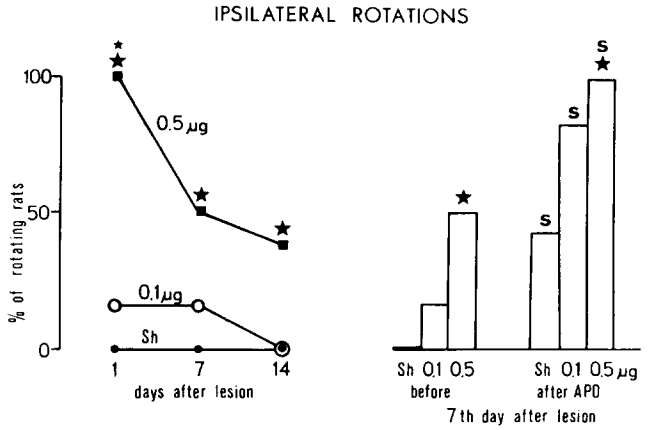

FIG. 4. Ipsilateral rotations induced by unilateral kainic acid lesions of the globus pallidus (GP) (left side); the effects of subcutaneous apomorphine (APO, 2.5 mg/kg) injections (right side). Filled circles—sham-operated rats Sh (r=14), open circles—rats lesioned with 0.1 μg/0.1 μl of kainic acid (n=6), filled squares—rats lesioned with 0.5 μg/0.1 μl of kainic acid (n=8), large asterisk—significant to sham-operated rats, small asterisk—significant to rats treated with 0.1 μg/0.1 μl of kainic acid, S—significant to the same rats before the apomorphine injection, differences were considered significant at $p<0.05$ and compared with Fisher's exact probability test.

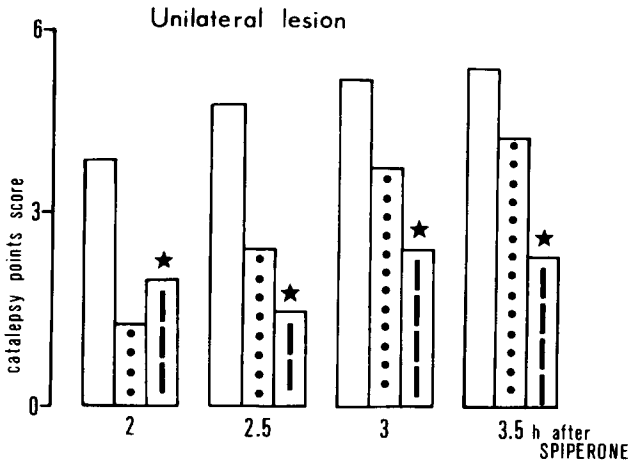

FIG. 5. The catalepsy induced by spiperone (0.2 mg/kg IP) measured in rats 15 days after globus pallidus (GP) lesions with kainic acid. Catalepsy was scored with a modified 6 points scale according to Delini-Stula and Morpurgo [10]; open bars—unilaterally (n=14) sham-operated rats (control rats for the group lesioned with 0.1 μg of kainic acid and for rats lesioned with 0.5 μg of the drug were pulled and are presented together), pointed bars—rats lesioned unilaterally with 0.1 μg/0.1 μl/GP of kainic acid (n=8), lined bars—rats lesioned unilaterally with 0.5 μg/0.1 μl/GP of kainic acid (n=8), asterisk—difference to sham-operated rats is significant at $p<0.05$ (Wilcoxon's two-sample test).

kainic acid injections into the globus pallidus are reported elsewhere [35].

DISCUSSION

It is generally accepted that akinesia, catalepsy and muscular rigidity are related to neostriatum and n. accumbens. It seems that the neostriatum is the main structure responsible for the increased muscular tone [2, 11, 12, 20, 21, 38], while akinesia and catalepsy or more generally the motility of animals seems to be dependent on n. accumbens [16, 23, 26, 36, 43]. We suppose therefore, that the behavioural effects produced by the globus pallidus lesions (akinesia, catalepsy, ptosis, hypothermia and muscular rigidity) which are similar to the results of a functional deficiency of dopamine synapses, are due to a decline of impulse flow which moves through the globus pallidus from neostriatum and n. accumbens. The directions of rotations observed: contralateral in the first short period after the lesion, i.e., in the same direction as after electric stimulation of the globus pallidus [18] and ipsilateral within the first days after the unilateral lesion of the globus pallidus agrees well with this opinion. Also several other data corroborate this conclusion. Similar behavioural effects: muscular rigidity (also particularly pronounced within hindlegs and back of rats), akinesia and catalepsy were observed after electrothermic lesions of the globus pallidus or after an inhibition [25] of the structure by GABA-mimetic substances like ethanolamine-O-sulphate (EOS, an inhibitor of GABAaminotransferase), muscimol and THIP (4,5,6,7-tetrahydroisoxazolo 5,4-c pyridin-3-ol) [25, 31, 33, 34, 37, 40, 45].

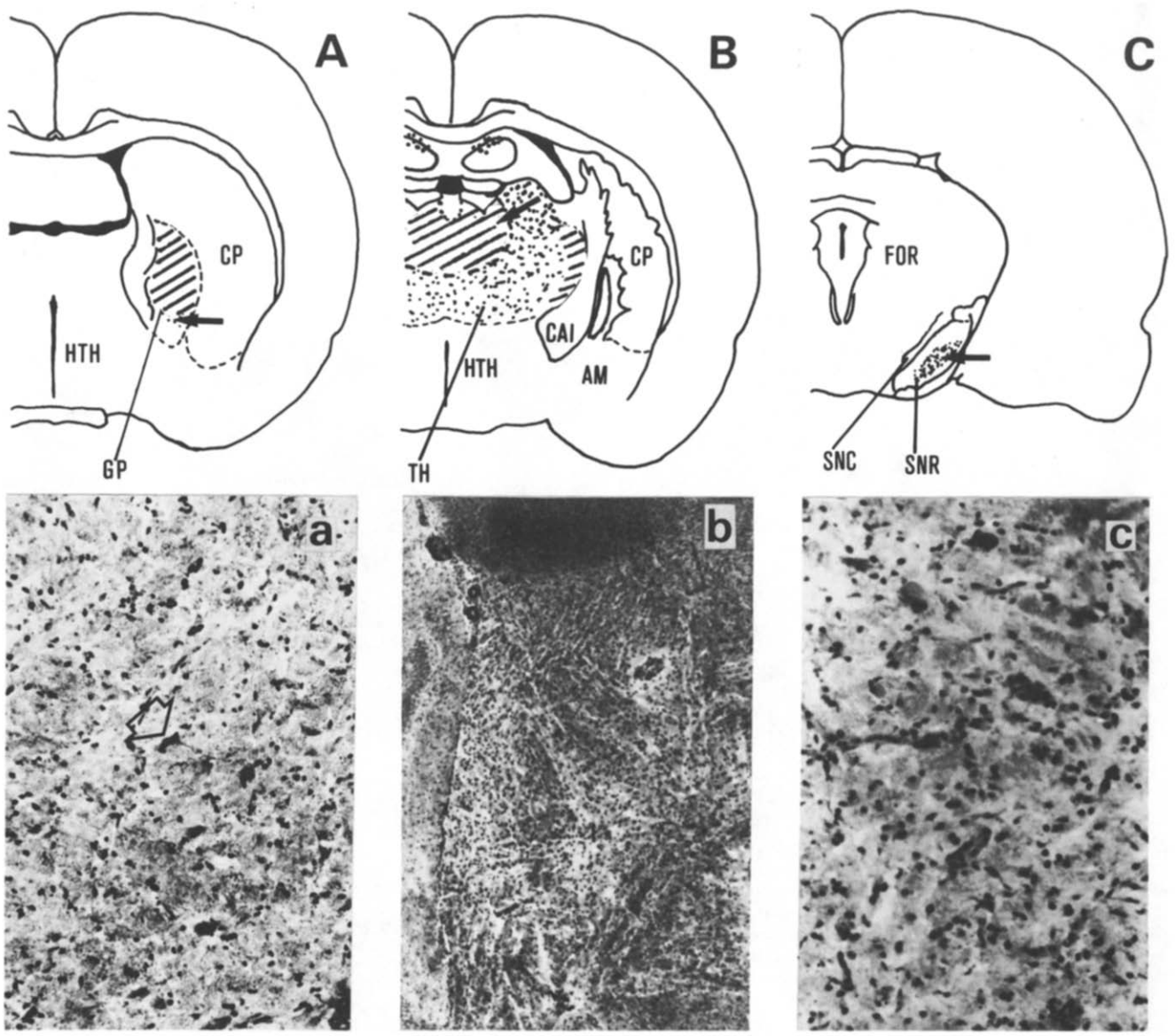

FIG. 6. The extension of lesions induced by kainic acid injections into the globus pallidus. A, B and C—schematic drawings of frontal sections of rat brain (atlas of König and Klippel [27]), a, b and c (lower part of the figure)—photographs of 10 μm frontal slices of the rat brain, stained with cresyl violet and luxol fast blue; A—the level of injection, B—the level of the largest extent of the thalamic lesion, C—the level of the substantia nigra lesion; a—lower part of globus pallidus (filled arrow at "A"), note: in the lower parts of the slide neurons which survived the kainic acid treatment might be seen (open arrow), (×140); b—dorsal thalamus (filled arrow at "B"), (×39); c—central part of the substantia nigra (filled arrow at "C"), (×187). Hatched fields in "A" and "B"—regions lesioned constantly, dotted fields in "B" and "C"—regions lesioned occasionally; AM—amygdala, CAI—capsula interna, CP—caudatus-putamen, FOR—formatio reticularis, GP—globus pallidus, HTH—hypothalamus, SNC—pars compacta of the substantia nigra, SNR—pars reticulata of the substantia nigra, TH—thalamus.

The majority of lesions induced by the kainic acid in areas distal from the injected region appeared irregularly (in a number of thalamic nuclei (compare with data reported by Carter and Fibiger [5]), some parts of substantia nigra, hippocampus, pyriform cortex and n. entopeduncularis) in spite of the constant presence of the described behavioural syndrome. Hence, these irregularly emerging lesions are not a prerequisite of the syndrome. Moreover, after bilateral electrothermic lesions of the globus pallidus where remote lesions seem to be unlikely, a nearly the same behavioural syndrome was observed [6, 7, 9, 45]. However, after electrothermic lesions never a sensory neglect to touch and pain limited to the skin of hindlegs and a marked hypersensitivness to touch on the other hand were reported. It may be that these behavioural effects are connected with the regularly associated to the globus pallidus lesion damage of some thalamic nuclei. The histological effects of kainic acid injections into the globus pallidus are discussed in details elsewhere [35].

Some of the effects of the globus pallidus lesions, i.e.,

akinesia and catalepsy were abolished by a subcutaneous injection of apomorphine but some of them, namely rigidity and ptosis remained unchanged. It is unlikely that the suppression of akinesia and catalepsy by apomorphine was transferred by strio-pallidal axons on pallidal neurons which persisted after the lesion, particularly because of the histological examination which indicates an almost total destruction of neuronal cells within the area innervated by the strio-pallidal axons (upper parts of the globus pallidus). Some neurons, however, in the narrow lower postero-medial parts of the structure (Fig. 6), survived the kainic acid treatment. Their cell bodies stained strongly for cholinesterase [35] and the localization of these neurons corresponds very well with that of the endings of neurons connecting n. accumbens with the globus pallidus [25]. These neurons may be assumed as part of cells receiving the projection from n. accumbens. After the kainic acid lesion of both kinds of cells (those receiving the striopallidal projection and partly also those acquiring the projection from the nucleus accumbens) the stimulation of the dopamine receptors of the n. accumbens by the endogenous dopamine seems insufficient to overcome the catalepsy which is due to the diminished impulse flow through the lesioned globus pallidus. The break of the catalepsy follows the overstimulation of the receptors by apomorphine only. Consistently with this assumption it was reported that the injection of apomorphine into the n. accumbens strongly enhances the motility of rats and counteracts the reserpine-induced akinesia and catalepsy [2, 16, 24, 36], and that the systemically injected amphetamine increases the spontaneous firing frequencies of globus pallidus neurons [3]. This assumption is supported further by the lack of influence of the bilateral injections of apomorphine into the n. accumbens on the reserpine-induced increase of muscle tone [2] while the injection of the drug into the neostriatum abolished the muscular rigidity [2]. The systemic injection of apomorphine (present results) was without effect also on the rigidity induced by the lesions of the globus pallidus, which supports in turn the completeness of the lesion of globus pallidus cells being the final station for the neostriatal projection.

The bilateral lesions of the globus pallidus produced a biphasic effect both in the untreated and in the spiperone-injected rats. In the first phase the damage provoked spontaneous akinesia ([6, 7, 9, 45] and present results), catalepsy and rigidity ([45] and present results) while in the second phase rats were hyperactive [6,7]. Consequently, when treated with neuroleptics the lesioned rats reacted in either phase variously, either, in the first phase with a catalepsy of similar intensity as sham-operated animals ([45] and present results) or, in the second phase with a weak catalepsy or a lack of catalepsy at all [6, 7, 9]. A similar effect was observed after unilateral lesion of the globus pallidus (Figs. 5 and 2A). However, after unilateral lesion the first phase was much shorter, lasted less than 1 week, while more than 2 weeks (Figs. 2A, B) or 3 weeks [9] after bilateral lesions of the structure. It is obvious that an unilateral damage is compensated for easier and quicker [15]. It seems, that either, at the end of the first week after unilateral lesion or within the third week after the bilateral damage of the globus pallidus, some compensatory mechanisms counteracted definitely the akinesia and catalepsy due to the lesion (rigidity and hunched-back posture remained [6]) or, which occurred frequently ([6, 7, 9, 45] and present results) the animal died. We can say that the compensatory mechanism substituted [15] a neuronal system which is not accessible to neuroleptics for the neuronal system open for dopaminergic drugs (suppression of the neuroleptic catalepsy by the globus pallidus lesions) ([6, 7, 9] and present results).

If we accept, according to Andén and Johnels [2], that the rigidity and the akinesia might be the result of a functional dopamine deficiency in the neostriatum and in the nucleus accumbens, respectively, it might be assumed that the globus pallidus in the next link of the neuronal chain forming the matrix of the central patterns of the increase of the muscle tone and akinesia, and perhaps also of the equivalents of these symptoms in Parkinson's disease. This conclusion is supported by the fact that globus pallidus lesions in humans alleviate the symptoms of Parkinson's disease [17,19].

One question remains open: why when even the distal link of the neuronal chain, including all main structures whose degenerations are seen in Parkinsonian patients (i.e., substantia nigra, neo- and palleostriatum), is broken the behavioural changes due to the lesion are relatively quickly compensated for in animals and not in patients? It might be speculated that (1) together with the main well known lesions also another neuronal, e.g., cortical [39] handicap is present which opposes the compensatory mechanisms in human beings, that (2) the lesions in the course of Parkinson's disease are much more disseminated as we presently suppose and finally that (3) it is not due to hazard that Parkinson's disease is an illness of older people whose neuronal plasticity is already limited. Presently we have only scarce evidence substantiating these speculations.

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