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Reserpine-Induced Rigidity in Rats: Drug Effects on Muscle Tone From Corpus Striatum and Nucleus Accumbens

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JOHNELS, B. *Reserpine-induced rigidity in rats: Drug effects on muscle tone from corpus striatum and nucleus accumbens*. PHARMACOL BIOCHEM BEHAV **19**(3) 463–470, 1983.—A study of the pathophysiological mechanisms of reserpine rigidity with the aid of a mechanographic method for the quantification of muscle tone. Apomorphine was used as a test substance to reduce reserpine rigidity by stimulation of dopamine receptors. Some experiments were made with additional drug treatment in an attempt to ascertain the dopaminergic specificity of the test. Apomorphine injected bilaterally to the corpus striatum has been shown to counteract the rigidity [6]. Microinjections of reserpine to corpus striatum induced rigidity with dominance in the hindleg ipsilateral to the side of injection. This rigidity was reduced by subcutaneous apomorphine. The effect of subcutaneous apomorphine on the rigidity was blocked by prior microinjection of trifluoperazine to the corpus striatum. Injections to nucleus accumbens were ineffective in all these respects. It is concluded that reserpine induces rigidity mainly by interference with the dopamine transmission in the corpus striatum.

Muscle tone Rigidity Reserpine Dopamine Corpus striatum Nucleus accumbens

RIGIDITY is one of the severely disabling motor symptoms in Parkinson's disease. It is noted on examination as an inability of the patient to voluntarily relax the muscles and as an increased muscle resistance to passive movements in a joint. The motor syndrome in parkinsonism is caused by degeneration of the dopaminergic neurons in the brain [13,26]. The main part of these nerve cells from the mesotelencephalic dopamine system [33,42]. On the base of morphological findings, this system may be considered to consist of two parts with different motor functions, the nigrostriatal and the meso-limbic pathways [42]. The previous finding that injection of apomorphine to the corpus striatum could relieve reserpine-induced rigidity in the rat [6] inspired to a more detailed analysis based on the hypothesis that the nigrostriatal but not the meso-limbic dopamine system controls muscle tone and that the rigidity is due to a specific nigrostriatal dopamine transmission defect. The ultimate goal of such studies is to find therapeutic means to treat the various symptoms of a patient more independently of each other, as this is highly needed today.

The present work consists of three parts: (a) A study of the effect produced by reserpine on the body posture and also on the rigidity as measured with a simple mechanographic method. The influence of the dopamine receptor stimulant drug apomorphine on these symptoms is described. (b) The effects on muscle tone in both hindlegs by bilateral or unilateral microinjection of reserpine into the brain. (c) A study of selective dopamine receptor blockage by microinjections in the corpus striatum and nucleus accumbens. The effects on apomorphine-induced alleviation to reserpine rigidity is described.

METHOD

Animals

One hundred and sixty-five male Sprague Dawley rats (200–300 g, Anticimex) were used. The animals were given food and water ad lib and the light was turned on between 6 a.m. and 6 p.m. The body temperature was monitored during the experiments (36–38°C) and assisted cooling or heating was provided when necessary.

Operations

All operations were performed in pentobarbital anesthesia on the day before the experiments. Intravenous injections were given through a catheter placed in the proximal end of the ligated right jugular vein.

In the experiments with local application of reserpine (n=40) or trifluoperazine (n=54) into the brain, stereotaxically guided implantation of guide cannulae (inner dia. 0.5 mm) was performed through bore holes in the skull bone. The cannulae were placed with their tips on the dura mater and fixed to the skull with acrylic cement. The injection cannulae (outer dia. 0.4 mm) were introduced into the brain through the guide cannulae their tips at the following coordinates: For the striatum: (AP 2.0, L+2.5, V 5.0) and for the nucleus accumbens: (AP 4.0, L±1.5, V 7.0) according to the atlas by Pellegrino and Cushman [34]. Injection rate: 1 μl/min. Volumes; striatum 2 μl, accumbens 1 μl. Histologic control of the location of the tips of the injection cannulae was made by microscopic inspection after at least two days of fixation of the brains in 4% formaldehyde solution.

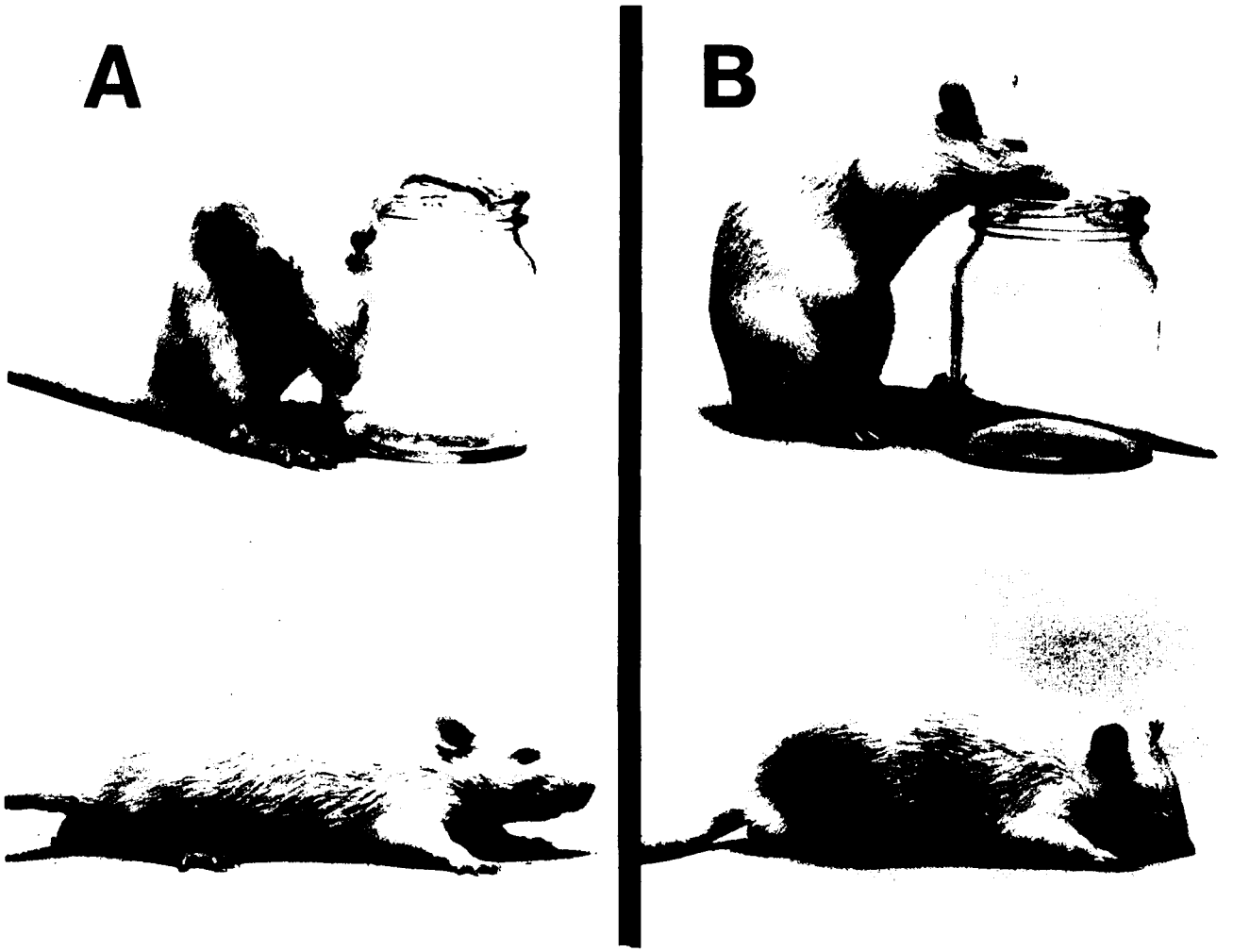

FIG. 1. Postural changes and akinesia after treatment with reserpine (10 mg/kg, IP) (B). There is flexion of the back and the extremities and a sustained lack of spontaneous movements. When the rat is standing on its hindlegs, the postural changes bear a close resemblance to those in parkinsonism. Normal rat in (A).

Drugs

Reserpine in form of the base (Serpasil Ciba-Geigy) and methiothepin maleate were dissolved in one drop of concentrated acetic acid, then diluted with 5.5 percent glucose solution and titrated to pH=4.0 with NaOH. Apomorphine (Apomorfin, ACO) carbidopa (MSD) and 5-hydroxotryptophan (Sigma) were dissolved in saline with addition of ascorbic acid (0.2 g/l) during cautios heating. Haloperidol (Haldol, Leo, 2.5 mg/ml) was taken from commercial ampoules. Trifluoperazine—HCl (Terfluzin, Leo-Rhodia) was dissolved in 0.9% saline. Prazosin-HCl (Peripress, Pfizer), clonidine (Catapresan, Boehringer-Ingelheim) and methysergide (Sansert, Sandoz) were dissolved in sterile water. Pentobarbital (Membumal, ACO) was given in a dose of 40 mg/kg, IP.

Procedure

The hindlimb muscle tension was recorded in conscious rats as the resistance to stretch of the calf muscle group measured by a mechanographic method. The animal was put into a plastic cylinder and its hindfeet fastened at the ankles. Muscle tone was assessed as the tension recorded during repetitive stretch procedures (dorsiflexion of the feet) and was expressed in percent of the tension during halothane anesthesia or in percent of maximal rigidity. The technique has been presented in detail in a preceding paper [29].

Statistical significances of the differences in muscle tone from that measured at the start of the recording and between groups of rats were calculated using variance analysis followed by t-test unless otherwise noted [46].

RESULTS

Systemic Treatment With Reserpine

Postural and autonomic effects were seen about 15 minutes after intravenous (3 mg/kg) and 30 minutes after intraperitoneal (10 mg/kg) treatment with a high dose of reser-

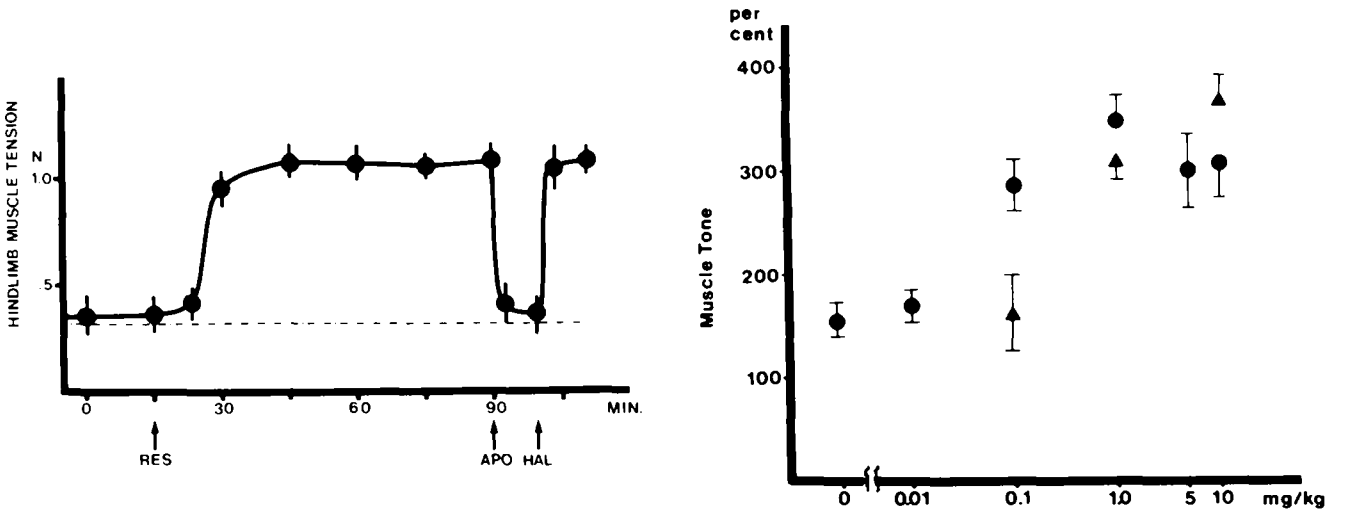

FIG. 2. A: Reserpine-induced rigidity. Reserpine (RES, 3 mg/kg, IV) was given after 15 min of recording of the calf muscle tension. A rapid increase of the tension followed within another 15 min. Subsequent injection of apomorphine (APO, 0.5 mg/kg, IV) quickly counteracted the rigidity. The effect of apomorphine was abolished when haloperidol (HAL, 3 mg/kg, IV) was given. Mean ± S.E.M. (n=6). The intersected line marks the tension measured in the completely relaxed muscles during halothane anesthesia. Tension in Newtons (N). 2B: Muscle tone after various doses of reserpine given IV (circles) or IP (triangles), 60 min in advance. The tone is noted in percent of the passive tension recorded during halothane anesthesia. Mean+S.E.M., n=6.

pine. The body posture was changed with appearance of flexion of the back (hunched back). The extremities were flexed and adducted and spontaneous movements disappeared as shown in Fig. 1. There was hyperfixation of the posture, so that the rats maintained for a long time an imposed upright standing on the hindlegs with the front paws on the top of a glass jar (catalepsy). If the rat was gently pushed to the side, there was no postural adjustment, but the rat fell slowly sideways. Protective and righting reflexes were quick, precise and adequate. A rat held upside down turned around and landed on its feet when released to free fall from as low a height as 160 mm. It thereafter resumed immobility. There was piloerection, closure of the eyes and accentuated bowel function. A slight body tremor could be palpated. Assessment of muscle tone by palpation was difficult due to interference by spontaneous changes of muscle tone on manipulation. The observed changes in muscle tone, posture and autonomic functions were completely counteracted by a subcutaneously given dose of apomorphine (1.0 mg/kg).

Mechanography. When the rats were placed in the mechanographic outfit, allowed to habituate for 20 minutes, and then treated with reserpine (3 mg/kg, IV), a quick rise of hindlimb muscle tension was recorded at the same time as the autonomic effects appeared, i.e., 15–20 minutes after treatment (Fig. 2A). A constant level of rigidity was seen for at least one hour whereafter the muscle tone fluctuated apparently dependant on sedation and exhaustion of the animal. Rigidity was present at about the same level when the rats were put in the mechanographic assembly, on various occasions, up to more than 24 hours after the injection of reserpine.

A subsequent injection of apomorphine (0.5 mg/kg, IV) abolished the rigidity for about 30 minutes following a few minutes of intense stereotyped behaviour (sniffing, licking, biting and struggling forward). These effects of apomorphine were quickly terminated by a subsequent injection of haloperidol (3 mg/kg, IV) and rigidity promptly reappeared. The rigidity was not clearly proportional to the administered dose of reserpine as seen in Fig. 2B. At low doses some rats failed to develop rigidity, while at high doses the muscle tone decreased due to a very marked sedation of the animal. Lower doses were needed on intravenous injection as compared to intraperitoneal administration.

Dopaminergic specificity. While reserpine quickly induced a stable level of rigidity, the effects on muscle tone of the dopamine receptor blocking drug trifluoperazine [28] were not so pronounced as is demonstrated by group A and B in Table 1. After a high dose, the muscle tone was slowly increased with a latency of about one hour and fluctuated to a much higher degree than with reserpine. The reserpine rigidity was dose-dependently reduced by apomorphine (Fig. 3). This effect could be totally blocked by previous injection of trifluoperazine (Table 1, group D). To check for effects on muscle tone by the activity of apomorphine on noradrenergic or serotoninergic receptors, prazosin (1–10 mg/kg), or methysergide was added to the reserpine treatments as seen in groups E and F. They did not, however, induce any significant blockade of the effects of apomorphine on the rigidity. Methiothepin (5–20 mg/kg, IP) had, likewise, no effect (Table 1, group G).

As it has been reported that treatment with 5-hydroxytryptophan reduces α-rigidity [38], this drug was given (50–100 mg/kg, IP) preceded by carbidopa (25 mg/kg, IP) to reduce the peripheral serotoninergic effects. There was a slight reduction of muscle tone (group H) which, however, was blocked if haloperidol (3 mg/kg, IP) was added to the treatment as seen in group I of Table 1.

The α_2-adrenoreceptor stimulant drug clonidine [5] was given to reserpine treated rats. In the dose range tried (0.01–

TABLE 1

HINDLIMB MUSCLE TENSION IN RATS. INDUCTION OF RIGIDITY AND THE COUNTERACTIVE EFFECT OF VARIOUS DRUGS

Group	No. of rats	Treatment (1)*	Tension N × 10 $^{-2}$	Treatment (2)†	Time for maximum efffect	Tension N · 10 $^{-2}$	Statistical significances (1)-(2)
A	10	None	43 ± 3	RES 10	2 hours	149 · 9	p < 0.001
B	8	None	50 · 2	TFP 3	2 hours	87 · 4	p < 0.001
C	6	RES 10	148 ± 11	APO 0.5	20 min	74 · 6	p < 0.001
D	8	RES 10 · TFP 3	130 · 6	APO 0.5	20 min	126 · 6	n.s.‡
E	8	RES 10 + PRZ 10	127 · 5	APO 0.5	20 min	67 · 8	p < 0.001
F	6	RES 10 + MET 10	125 ± 7	APO 0.5	20 min	71 · 6	p < 0.001
G	9	RES 10 · METI 20	114 · 11	APO 0.5	20 min	58 · 10	p < 0.001
H	8	RES 10	132 ± 11	CDP 25 · 5HTP 50	1 hour	89 · 18	n.s.‡
I	6	RES 10 · HAL 3	132 ± 3	CDP 25 · 5HTP 50	1 hour	139 · 3	n.s.‡

*RES,Reserpine; TFP,Trifluoperazine; APO, Apomorphine; PRZ,Prazosin; MET,Methysergide; METI,Methiothepine; CDP,Carbidopa; 5HTP,5-Hydroxytryptophan; HAL,Haloperidol; Dose in mg/kg, IP Treatment (1) was given one hour before start of recording. Mean tension ± S.E.M.

†Doses in mg/kg, IP except APO that was given SC. The hindlimb muscle tension was measured at the time for maximum effect.

‡p Values from two tail distribution, p > 0.05 is regarded as unsignificant (n.s.).

0.5 mg/kg, IP) and 1–10 μg per side intrastriatally) the effect on the rigidity was ambiguous. On the higher dose the rats were intensely agitated and moved to and fro with jerking movements.

Microinjections to the Corpus Striatum and Nucleus Accumbens

Reserpine. Previous experiments have shown that the reserpine induced rigidity could be alleviated by local application of apomorphine to the corpus striatum but not when injected to the nucleus accumbens [6]. It was therefore thought to be of interest to see if rigidity could be evoked by injection of neuroleptic drugs to the corpus striatum. Injection was made bilaterally by small quantities of reserpine or solvent into the corpus striatum (2×80 μg/2 μl, n=32) or of reserpine into the nucleus accumbens (2×80 μg/1 μl, n=10). The muscle tension was recorded for 90 minutes, and the maximal value was noted and compared to that during halothane anesthesia at the end of the experiment. To those rats that developed rigidity, apomorphine (0.5 mg/kg, SC) was given to test for the effects of dopamine receptor stimulation. A significant degree of rigidity was found mostly when the injections were made in the midportion of the corpus striatum as seen in Fig. 4A and B. No rigidity was found when reserpine was injected into the nucleus accumbens (Fig. 4B) or close to the globus pallidus or after injection of solvent into the corpus striatum. In the 18 cases that developed rigidity the muscle tone was reduced after treatment with apomorphine (Fig. 4B, treatment 2a and 2b).

Injections of reserpine were also given unilaterally (80 μg/2–4 μl, n=10) to the right or left corpus striatum. The same volume of solvent (acetic acid and glucose) was injected on the contralateral side. Within 2 hours time, the animals appeared slightly bradykinetic and had a tendency to turn towards the side of reserpine injection. Mechanography revealed an increase of hindleg muscle tone, which was most pronounced on the side where the reserpine injection had been made (Fig. 5A). Subsequent treatment with apomorphine (0.5 mg/kg, SC) reduced the rigidity (Fig. 5B) and induced rotation of freely moving animals ipsiversive to the side of injection of reserpine. One to two days later some rats (7/10) showed a contraversive rotation after apomorphine.

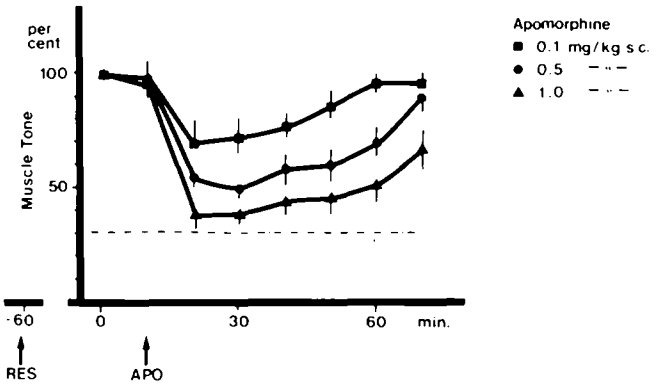

FIG. 3. Reduction of reserpine rigidity by various doses of apomorphine. Recording was started 60 minutes after treatment with reserpine (10 mg/kg, IP) and the tension measured (1.23 Newtons) was set to 100 percent. A subsequent injection of apomorphine dose-dependently lowered the muscle tone. Mean+S.E.M., n=6. The intersected line marks the tension measured during halothane anesthesia.

Local Application of Trifluoperazine Bilaterally to the Corpus Striatum or Nucleus Accumbens

These experiments were performed to see if microinjection of a dopamine receptor blocking agent to either of these nuclei would abolish the effect of systemic apomorphine on reserpine rigidity. From Fig. 6 it can be seen that trifluoperazine microinjected to the corpus striatum blocked the effect of apomorphine in a dose dependent way. The block was complete after injection of 20 μg to each side (Fig. 6A). The same doses injected intravenously gave no or only slight reduction of the effect of apomorphine (Fig. 6B). Bilateral injections of trifluoperazine (10–20 μg/1 μl) to the nucleus accumbens did not block the effect of apomorphine on muscle tone (Fig. 6C). Given as single treatment in the brain, trifluoperazine (5–20 μg/2 μl, 2 hours, corpus striatum, bilat-

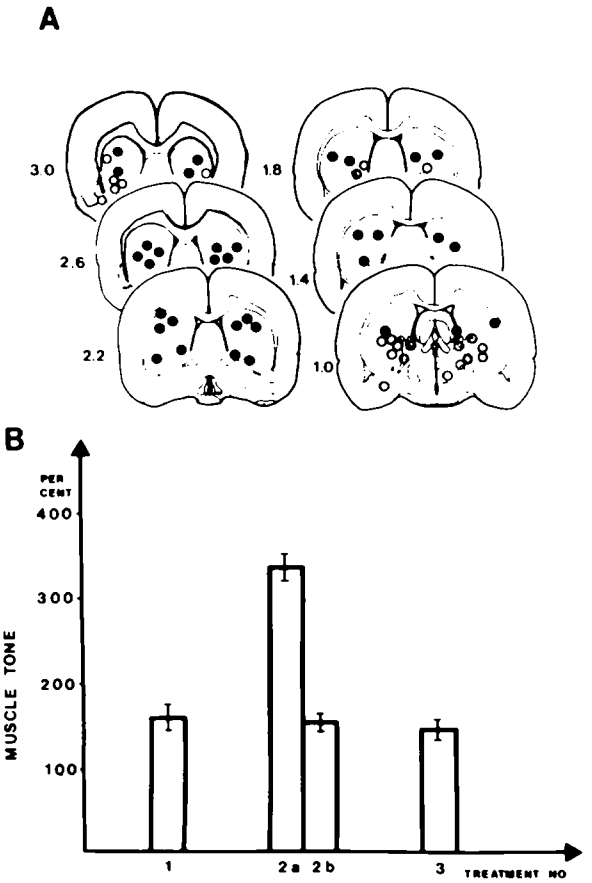

FIG. 4. Microinjection of reserpine. Reserpine (2×80 μg/2 μl) was injected bilaterally into the corpus striatum and adjacent areas. The tips of the injection cannulas were located in later histological sections of the brain. A: The position of the tip in those cases where a significant degree of rigidity was developed are marked with filled circles whereas those cases where the injections were without effect on muscle tone are marked with open circles. Numbers indicate millimeters anterior of bregma. B: Muscle tone after bilateral injection of reserpine to the brain. 1. control group (solvent 2×2 μl, corpus striatum n = 10), 2a. reserpine (2×80 μg/2 μl, corpus striatum, n 18), 2b. Subsequent treatment of rats in 2a with apomorphine (0.5 mg/kg, SC), 3. reserpine (2×80 μg/μl, nucleus accumbens, n = 10). The muscle tone is shown in percent of the tension recorded during halothane anesthesia (relaxed muscle). Statistical significance 2a 2b, $p<0.001$.

erally) did not cause significant rigidity as judged by inspection and palpation of the animals (n = 30).

DISCUSSION

In the search for a deepened insight in the pathophysiological mechanisms of Parkinson's disease and a better symptomatic therapy there is need for relevant animal models of the disease. Up to now the only such model of Parkinsonism is the animal that has been treated with a high dose of reserpine [14,31], although other models, as the animal with bilateral 6-hydroxy-dopamine-induced degeneration of the ascending dopamine pathways may show some of the symptoms (such as akinesia) but no consistent rigidity [43, 44, 45].

The main disadvantage with reserpine is that this drug has extensive, partly unknown, pharmacologic effects. It lowers

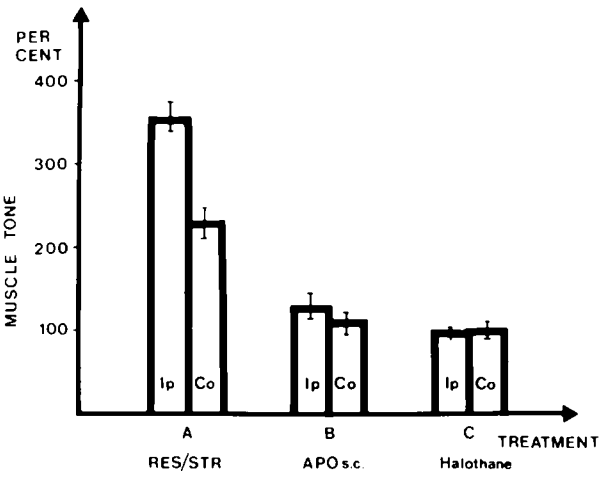

FIG. 5. Calf muscle tone after unilateral injection of reserpine to corpus striatum. Ip: ipsilateral to the side of injection. Co: contralateral side. A. RES/STR: reserpine (80 μg/2 μl, corpus striatum). B. APO SC the effect of a subsequent injection of apomorphine (0.5 mg/kg, SC) on the reserpine-induced rigidity in A. C. Muscle tone was set to 100 percent during halothane anesthesia (relaxed muscles).

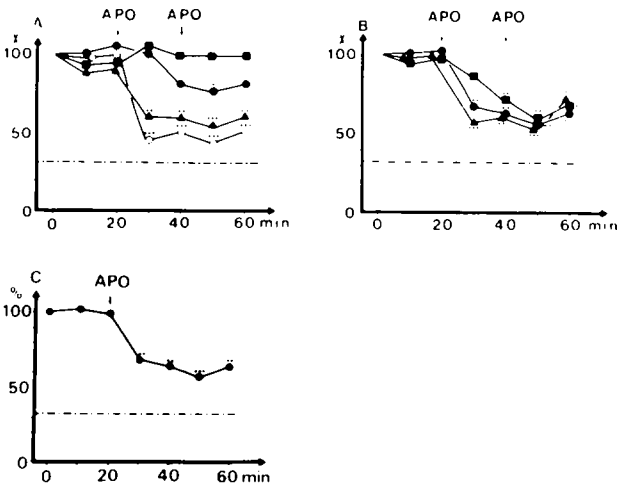

FIG. 6. Intrastriatal (A) and intravenous (B) or intra-accumbens (C) injection of trifluoperazine (TFP). Blocking effect on the degree of reduction of reserpine-induced rigidity obtained by treatment with apomorphine. Reserpine (10 mg/kg, IP) was given to induce rigidity and 20 min later bilateral microinjections of TFP (2×2 μl) or saline (control) to the corpus striatum (A) or intravenous injections of TFP (B) were performed to block the dopamine receptors. The rats were then put in the mechanograph. After twenty and forty minutes of recording they were given apomorphine (0.5 and 1.0 mg/kg, SC, respectively) to test for dopamine-dependent reduction of muscle tone (arrows). The muscle tone is expressed in percent of the reserpine-reduced rigidity as measured at the start of recording (see Table 1). ■ TFP 2×20 or 40 μg; ● TFP 2×10 or 20 μg; ▲ TFP 2×5 or 10 μg; ○ saline. Statistical significances of the differences in muscle tone from the rigid state (start of recording) is marked as follows: $***p<0.001$, $**p<0.01$, $*p<0.05$. Mean square within cells; 307.83, $df = 343$.

the brain content of all monoamine transmitter substances [11, 14, 39]. There are, however, several factors indicating that the reserpine-induced Parkinsonism might depend on the same mechanisms as the motor symptoms of the disease, i.e., mainly loss of dopamine transmission [17,26]. Reserpine-induced parkinsonism is clinically indistinguishable from the disease [21,24] and can likewise be treated with l-dopa [20] as is the case in animals [13]. Thus reserpine rigidity in the rat might be a relevant model of Parkinsonian rigidity and reveal some of the generating mechanisms.

The postural changes (Fig. 1) and the reflex responses to stretch of the rigid muscle in the reserpine-treated rat are closely similar to those found in Parkinson's disease [29]. Lesions of the striatal nuclei has been shown to abolish the rigidity [8] as did treatment with l-dopa [39]. Thus, it could be assumed that the reserpine rigidity was caused by interaction with striatal catecholamine transmission. Dopaminergic stimulation of the nucleus accumbens septi evoked hyperlocomotion in reserpine-treated rats [27,30], while stimulation of the corpus striatum evoked stereotyped, hyperkinetic movements [23]. The close association between postural and locomotor functions [37] raised the question whether the nigrostriatal or mesolimbic parts of the ascending mesotelencephalic dopamine system [42] were involved in reserpine rigidity. Thus, microinjections of drugs were given into terminal areas of these two systems, the corpus striatum and nucleus accumbens. Apomorphine, a potent dopamine receptor stimulant [3,16], abolished the reserpine rigidity when injected bilaterally to the corpus striatum but not when given into the nucleus accumbens or when haloperidol had been given in advance [6]. Thus, there was indication of a differential control of muscle tone and locomotion as has been proposed for the deficits of postural control and voluntary movement in parkinsonian patients [32].

From the finding presented in Table 1 and Fig. 3 it seems more likely that the effects on muscle tone by reserpine and apomorphine are generated by interaction with the dopaminergic rather than with the adrenergic or serotoninergic functions in the brain. There was a slight reduction of muscle tone after treatment with 5-hydroxytryptophan, the precursor substance to serotonin, but this effect might have been caused by interaction with the dopaminergic transmission as it was cancelled by prior injection of trifluoperazine, a potent catecholamine receptor antagonist [9,28].

A high dose of methysergide or methiothepin did not change the effect of apomorphine. These drugs block peripheral serotoninergic receptors, but it is admittedly uncertain if methysergide had any effects within the central nervous system [7]. At present there is, however, no other drug known to the author that more selectively blocks central 5-HT receptors. Prazosin is known to be a rather selective α_1-adrenergic receptor blocking agent [12]. Moderate or high doses of this drug did not block the response on reserpine-rigidity elicited on systemic administration of apomorphine. This points to that these dose dependent effects by apomorphine are due to stimulation of dopamine receptors and consequently that reserpine rigidity is mainly caused by a deficiency of the dopamine transmission. It is notable that the rigidity developed rather quickly (Fig. 2A) when the monoamine levels in the brain still are quite high [4]. Autonomic effects were seen at the same time. One explanation to these findings may be that the effect on monoamine transmission precedes the effect of diffusion of liberated amines and the metabolic degradation, as do the (receptor mediated?) inhibitory effects on the dopamine synthesis [15]. Influences from serotoninergic and noradrenergic pathways thus cannot be excluded when reserpine is given systemically, especially in the early phase of rigidity as these monoamines are known to exert strong influences on spinal nervous functions and might change hindlimb muscle tone on the segmental level [2].

The next step thus was to ascertain that reserpine exerts its action on the dopamine terminals in the striatum. Rigidity could be evoked by local microinjection of reserpine bilaterally into the corpus striatum. That a high dose was necessary corresponds to earlier findings [22]. This dose would have caused rigidity also if injected intravenously (Fig. 2B), and the reserpine might thus have caused widespread effects when distributed to other parts of the nervous system by the circulation. On the other hand, it might be suspected that there will be a slow release into the circulation when reserpine is injected into the brain, and that only small amounts will reach other parts of the brain. Chemical substances tend to diffuse slowly when injected to the brain and are normally found within a radius of a few millimeters when the injected volume is less than 5 μl [35, 40, 47]. Reserpine is quickly metabolized to rather inert substances [25,39], except for a very small fraction that is bound to the monoamine nerve terminal granules [19,36] where it exerts its supposed action by disrupting the transmitter storage function [10, 14, 18]. It might therefore be assumed that the conditions are relatively good for a localized action and a restricted spread of the functional effects of this drug. The finding that injections of reserpine to nearby structures were ineffective as to the nucleus accumbens (Fig. 4B, treatment No. 3) or to the globus pallidus (Fig. 4A) lend further weight to the assumption above. That the reserpine-induced rigidity was caused by a specific action on the dopaminergic mechanisms is shown by the counter-active effect on the rigidity by the subsequent treatment with apomorphine (Fig. 4, treatment 2b). Unspecific noxious influences on the corpus striatum such as too high dose of certain drugs [1], lesions, acid solvents (Fig. 4, treatment 1), ascorbic acid and potassium chloride tend to somewhat reduce the reserpine rigidity (data not shown).

Unilateral injections of reserpine (80 μg/2–4 μl) to the corpus striatum produced an increase of muscle tone in the ipsilateral hindleg that was reduced on treatment with apomorphine (Fig. 5). There was also a tendency to "rotate" ipsiversively with the hindlegs relatively immobile when apomorphine was given a couple of hours after unilateral reserpine treatment. These asymmetrical motor effects give additional evidence for a specific effect on dopamine transmission localized to the side of the injection of reserpine. The autonomic effects usually seen on systemic treatment (closure of the eyes, piloerection, loss of temperature regulation) were weak or absent, which speaks in favour of a slow diffusion of reserpine in the brain.

If the rigidity seen after systemic treatment with reserpine was due to loss of activation of dopamine receptors in the corpus striatum, it should be possible to block the effect of systemic apomorphine on this rigidity by local application of a dopamine receptor antagonist to these nuclei. Thus, bilateral injections of trifluoperazine were made. Injections to the corpus striatum blocked the effect of systemic apomorphine in a dose-dependant manner (Fig. 6A) while injections to the accumbens or intravenously were less effective (Fig. 6B and C). Trifluoperazine in a high dose augmented the muscle tone (Table 1, group B), but this drug was less efficacious than reserpine, and the effect appeared slowly with a latency

of one hour. The apparent paradox that trifluoperazine could block the effect of apomorphine without inducing obvious rigidity might tentatively be explained by the suggestion that it is much more difficult to block the intrinsic dopamine transmission profoundly than the effects of extrinsic apomorphine.

To sum up, several different methods have been applied in an attempt to find the role of dopamine transmission in reserpine rigidity. None of these methods could alone provide conclusive evidence. On the other hand, all the findings point to a crucial role for striatal dopamine transmission in the regulation of muscle tone. No effects on muscle tone were found from the dopamine receptors in the nucleus accumbens. Thus, there is evidence for a differential control of muscle tone and locomotion from the nigrostriatal and the mesolimbic dopamine neuron systems respectively. The reserpine-treated rat can serve as an animal model for elucidating these mechanisms. These findings might be of importance in the work to create more specific treatment for the different motor symptoms of Parkinson's disease.

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