Pharmacology Biochemistry & Behavior, Vol. 21, pp. 825-831, 1984. © Ankho International Inc. Printed in the U.S.A. 0091-3057/84 $3.00 + .00

The Role of the GABA Mechanisms of the Globus Pallidus in Mediating Catalepsy, Stereotypy and Locomotor Activity

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Received 12 April 1984

OSSOWSKA, K., K. WĘDZONY AND S. WOLFARTH. *The role of the GABA mechanisms of the globus pallidus in mediating catalepsy, stereotypy and locomotor activity.* PHARMACOL BIOCHEM BEHAV **21**(6) 825–831, 1984.—Muscimol, picrotoxin and bicuculline were injected bilaterally through permanently implanted cannulae into either anterior (GPa) or posterior parts of the globus pallidus (GPp) of rats. Both the muscimol injected into the GPa and the picrotoxin injected into the GPp abolished or strongly inhibited spiperone (0.2 mg/kg, IP)-induced catalepsy. Muscimol alone (25–200 ng/0.2 μl/GP) injected into the GPa evoked a dose-dependent biphasic effect: at first catalepsy (throughout 7.3 min), and then a long-lasting (more than 2 hr) locomotor stimulation and stereotyped sniffing. Muscimol (200 ng/GP) injected into GPp inhibited both the spontaneous motility and amphetamine-induced hyperactivity. Picrotoxin (200 and 400 ng/GP) injections into GPa and GPp produced an increase of the locomotor activity as well as stereotyped sniffing. Picrotoxin started to block muscimol hyperactivity when its own stimulatory action disappeared, thus also for picrotoxin the second phase of action could be detected. The globus pallidus is shown to be a relay station of impulses mediating neuroleptic catalepsy. Furthermore, it is suggested that behavioural changes induced by muscimol resulted from the action of the drug on at least 2 different neuronal systems, both being controlled by GABA receptors. One of them seems to be responsible for inducing neuroleptic-like catalepsy, and the other one for the hyperactivity and blockade of spiperone-catalepsy.

Globus pallidus GABA mechanisms Catalepsy Stereotypy Locomotor activity

FOR a long time it has been believed that the globus pallidus (GP) is a key structure of the extrapyramidal system [10] involved, together with the substantia nigra, in Parkinson's disease [8, 9, 12, 17, 19]. Recently many reports indicate [2, 13, 21, 25, 30] that the pars reticulata of the substantia nigra is the most important output structure of the extrapyramidal system. Nevertheless, these are the GP output fibers and not the nigral ones that are surgically interrupted in order to alleviate Parkinson's disease symptoms [8, 9, 17]. The GP contains large amounts of γ-aminobutyric acid (GABA) [15, 17, 20], and of a GABA synthesizing enzyme, GABA-decarboxylase (GAD) [7]. It has been reported that both GABA and GAD are decreased within the GP in the course of Parkinson's disease and Huntington's Chorea [17–19]. Injection of GABA agonist, e.g., muscimol into the GP does not produce, however, clearcut behavioural effects. It has been found that muscimol injected into the GP of rats evokes either a catalepsy itself [16,20] or catalepsy followed by a locomotor stimulation [24–26] or no effects at all [6]. GP is anatomically a heterogenous structure [11], and it is suggested by Scheel-Krüger and co-workers [25,26] that this may be the cause of either a catalepsy or the lack of effect.

The aim of our study was to elucidate the above mentioned discrepancies and to specify the role of different parts of the globus pallidus in mediating catalepsy, stereotypy and locomotor activity. We intend to demonstrate that the globus pallidus is a relay station for impulses mediating neuroleptic catalepsy and that muscimol induces biphasic changes in the rat behaviour. Most probably, the changes result from the action of the drug on at least 2 functionally different neuronal systems. One of them seems to be responsible mainly for a cataleptic phase of the muscimol action, and the other one for the subsequent hyperactivity phase.

METHOD

Experiments were carried out on male Wistar rats, weighing from 180 to 300 g at the time of surgery. The rats were stereotaxically implanted with stainless steel guide cannulae (ext. diameter 0.4 mm) under a pentobarbital anaesthesia (Vetbutal, Biowet, Poland, 30 mg/kg IP). The cannulae were introduced bilaterally to the upper limit of the globus pallidus (GP) and fixed to the skull with dental cement. After the surgery the rats were housed in separate wire cages (21×21×24 cm) with free access to water and food pellets.

Compounds Used

Muscimol (25, 50, 100 and 200 ng/GP, Serva, Feinbiochem, Heidelberg, FRG), THIP (2.5 μ/GP, 4,5,6,7-tetrahydroisoxasolo- (5,4-c)piridin-3-ol, H. Lundbeck Co., Kobenhavn), picrotoxin (200 and 400 ng/GP, Sigma), bicuculline methiodide (400 ng/GP, Pierce, Rockford, IL,

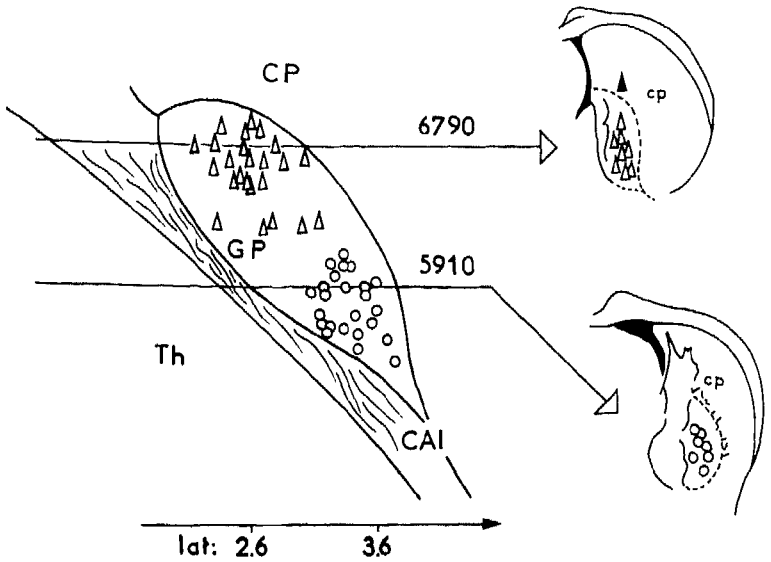

FIG. 1. A diagrammatic presentation of the localization of the cannulae tips on horizontal and frontal sections of the rat brain according to the König and Klippel atlas [14]; open triangles—cannulae tips in the anterior part of the globus pallidus (GPa), open circles—tips located in the posterior part of the globus pallidus (GPp), filled triangle—the localization of cannula tip outside the globus pallidus in the caudate-putamen—note that the injection through this cannula evoked slight and delayed effects only. A part of histological results is omitted because of the clarity of the picture. CAI—capsula interna, GP—globus pallidus, Th—thalamus, CP—caudatus-putamen.

USA) were dissolved in 0.2 μl of sterile redistilled water (also used as a control solution) and injected successively into both globi pallidi through an internal cannula (ext. diameter 0.3 mm) protruding from the guide cannula by 1.3 mm. The rats were divided into 2 groups: (1) those in which the tip of the internal cannula was directed into the anterior and medial parts of GP (GPa) (coordinates [14] of the tip A=6.7; L=2.2; H= −0.8) (Fig. 1) and (2) those in which the drugs were injected into the posterior part of the GP (GPp) (coordinates A=5.9; L=3.3; H= −1.2). The pH-values of the injected solutions were within the range 4.95–5.98. The Hamilton syringe having a total volume of 1 or 2 μl was used and the injection rate was 0.2 μl/1 min. The internal cannula was left inside the guide cannula until 1 min after the injection. Spiperone (0.2 mg/kg IP, Janssen Pharmaceutica) dissolved in 0.1 M tartaric acid was administered either 1.5 hr before intrapallidal injections of muscimol or 2 hr before intrapallidal injections of picrotoxin. Apomorphine (1.0 and 2.5 mg/kg SC, Sandoz) was injected either 10 min after intrapallidal injections of picrotoxin or 1 hr after intrapallidal injections of muscimol. Amphetamine (1.5 mg/kg SC, d-amphetamine sulphate, Smith, Kline and French) was injected 30 min before the muscimol administration.

Behavioural Studies

Experimental sessions started between weeks 1 and 2 after the surgical implantation of the guide cannulae, and were repeated twice on the same animal (with the compound tested and the control solution), spaced out at least 4 days apart (most often more than 1 week apart) and carried out between 8 a.m. and 3 p.m. The number of rats in experimental groups was, if not stated otherwise, 5–8.

The locomotor activity was measured after a 0.5–1.0 hr adaptation period with photoresistor actometers (two-light beams, two photoresistors) in which the rats were placed individually. The number of counts was recorded every 30 min or sometimes every 10 min. The assessment of stereotyped behaviour was carried out in reference to the number of animal revealing stereotyped sniffing, licking or gnawing. For the stereotyped behaviour rats were observed separately in the same kind of wire cages in which they were housed.

Catalepsy was scored by the modified method of Wirth *et al.* [28]. The modification consisted in placing rats with their forepaws on a 9 cm high cork and measuring the time throughout which they maintained this unnatural position. Estimations of the muscle tone were based on the method used by clinicians, consisting in evaluation of the muscle tone by the touch, and of the resistance to flexions opposed by extremities.

After the experiment all the rats were killed by an overdose of pentobarbitone, their brains were removed, and fixed in the 10% formaldehyde solution. The localization of the internal cannulae tips was examined histologically by means of directly taken photographs of unstained frozen brain slices (60 μm). All the animals in which the cannulae tips were located outside the globus pallidus, or were placed even within this structure but distinctly asymmetrically, were eliminated from the experiment.

A statistical comparison of different groups of rats was carried out by Student's *t*-test or by Fisher's exact probability test.

RESULTS

On the basis of histological examining of the localization of the cannulae tips the rats were divided into 2 groups: (1)

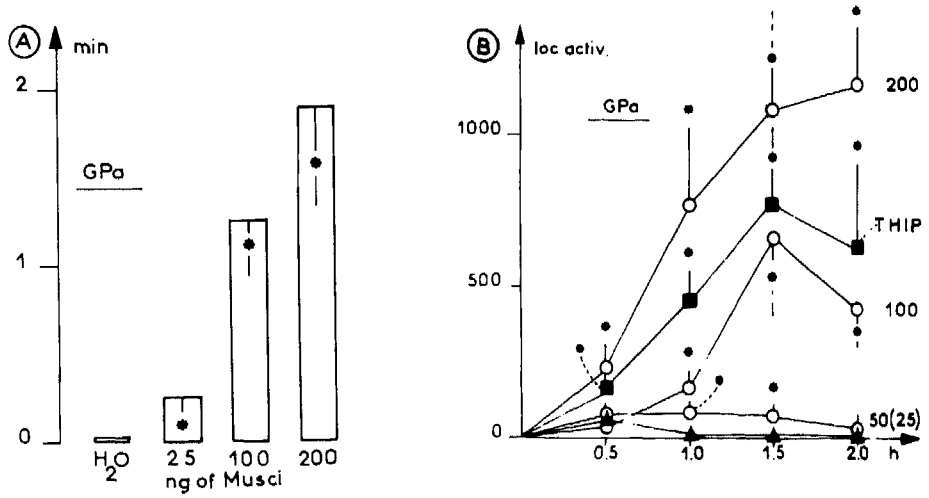

FIG. 2. The behavioural effects of bilateral injections of muscimol (Musci) and THIP into the anterior part of the globus pallidus (GPa), A—catalepsy induced by bilateral injections of muscimol (25, 100, 200 ng), catalepsy was scored with a modified method of Wirth *et al.* [28]; the ordinate—duration of unnatural cataleptic position in min. B—the locomotor activity induced by bilateral injections of muscimol (25, 50, 100, 200 ng/0.2 μl) and THIP (2.5 μg/0.2 μl). Filled triangles—solvent-treated rats, open circles—muscimol-treated rats, filled squares—THIP-treated rats. Doses of muscimol are expressed in nanograms—ng, the asterisk—significant difference to control rats at $p<0.05$ (Student's t-test).

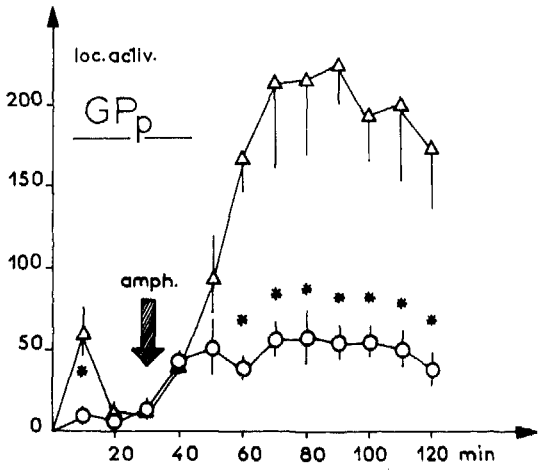

FIG. 3. The effect of bilateral muscimol (200 ng/0.2 μl) injections into the posterior part of the globus pallidus (GPp) on the locomotor activity induced by peripheral administration of amphetamine (amph) (1.5 mg/kg SC). Circles—combined injections of muscimol into the GPp and amphetamine (SC, 30 min after muscimol), triangles—combined injections of solvent into the GPp and amphetamine (SC). The asterisk—significant difference between both groups at $p<0.05$ (Student's t-test).

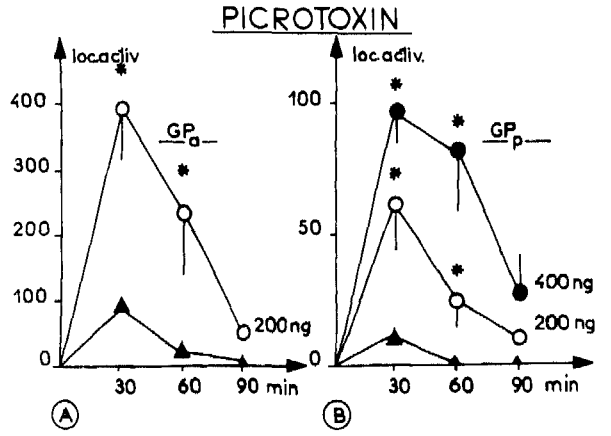

FIG. 4. The locomotor activity induced by bilateral injections of picrotoxin into the: A—anterior part of the globus pallidus (GPa), B—posterior part of the globus pallidus (GPp). Filled triangles—solvent treated, control rats, open circles—picrotoxin 200 ng, filled circles—picrotoxin 400 ng, the asterisk—significant difference to control rats at $p<0.05$ (Student's t-test).

those in which the drugs were administered into the anterior part of the GP (GPa), i.e., between A=6860 and A=6280, according to the atlas of König and Klippel [14] (Fig. 1), and (2) those which received the drugs into the posterior part of GP (GPp), i.e., between A=6060 and A=5780 (Fig. 1).

The Effects of Muscimol

Muscimol injected into the GPa (25, 50, 100 and 200 ng/GPa) produced a biphasic effect: a catalepsy (Fig. 2A) within a short period (7.3 min±1.73 after 200 ng/GPa) starting immediately after the end of injection, and a strong, dose-dependent increase of the locomotor activity (Fig. 2B) accompanied by an intense stereotyped sniffing in the next long-lasting phase. The cataleptic reaction depended also on the dose (Fig. 2A). Together with the catalepsy, increasing of the muscle tone, particularly in the hind legs, a fine

TABLE 1

THE EFFECTS OF BILATERAL INJECTIONS OF MUSCIMOL (Musci 200 ng) INTO THE ANTERIOR PART OF THE GLOBUS PALLIDUS (GPa), OR PICROTOXIN (Pi 400 ng) INTO THE POSTERIOR PART OF THIS STRUCTURE (GPp) ON THE APOMORPHINE (APO)-INDUCED STEREOTYPY

	GPa				GPp					
	Musci 200 ng	H_2O	Musci 200 ng	Pi 400 ng	H_2O	Pi 400 ng	H_2O	Pi 400 ng	H_2O	Pi 400 ng
Stereotypy	H_2O	APO 2.5 mg/kg		H_2O	APO 0.5 mg/kg		APO 1.0 mg/kg		APO 2.5 mg/kg	
Sniffing	10(10)*	10(10)	10(10)	5(5)	5(5)	5(5)	5(5)	5(5)	5(5)	5(5)
Licking	0(10)	7(10)	0(10)†	0(5)	1(5)	3(5)	4(5)	0(5)†	5(5)	0(5)†
Gnawing	0(10)	7(10)	0(10)†	3(5)	0(5)	4(5)†	1(5)	5(5)†	5(5)	5(5)

*The figure without brackets denotes the number of rats in which a given symptom was observed, while the figure in brackets denotes the number of rats used.

†Significant ($p<0.05$) to the H_2O + APO-treated group according to Fisher's exact probability test.

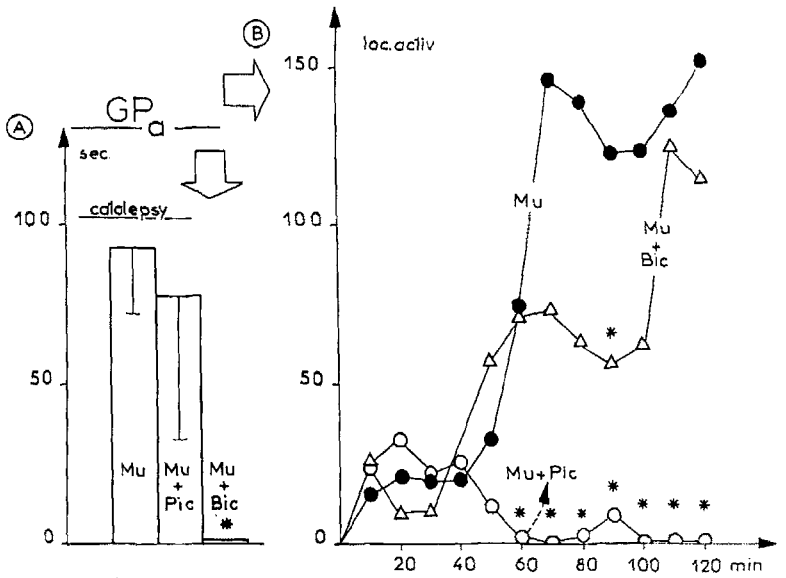

FIG. 5. The effects of bilateral injections of bicuculline and picrotoxin into the anterior part of the globus pallidus (GPa) on catalepsy (A) and locomotor activity (B) induced by muscimol. Bicuculline (Bic, 400 ng/0.2 μl) and picrotoxin (Pic, 200 ng/0.2 μl) were injected 10 and 30 min before muscimol (Mu, 100 ng/0.2 μl/GPa) respectively. The asterisk—significant difference to muscimol-treated rats at $p<0.05$ (Student's t-test).

tremor of the whole body and a very slight ptosis or no ptosis at all were observed. Throughout the period of bigger locomotor activity in a few rats sporadic episodes of licking and/or gnawing were also observed. THIP, another agonist of the GABA receptor, evoked the same effects (Fig. 2B).

In the rats in which the muscimol injections were directed markedly asymmetrically, e.g., one cannula in the GPa and the other in the GPp, or outside the GP at all (Fig. 1), neither the cataleptic phase nor the enhanced locomotor activity phase were observed. When the cannulae were placed in the narrow, most dorsal region of the GPa or between the nucleus caudatus-putamen and the GPa, a slight enhancement of the locomotor activity was recorded, about 1.5 hr after the injection of muscimol only (Fig. 1).

Muscimol (200 ng) injected bilaterally into the GPp evoked neither catalepsy nor an enhancement of the locomotor activity: it inhibited only the spontaneous motility within the first 10 min after the injection (Fig. 3). However, muscimol injected into the GPp inhibited strongly the amphetamine-induced hyperactivity (Fig. 3).

The Effects of Picrotoxin

The bilateral injections of picrotoxin into both GPa and GPp enhanced the locomotor activity of rats (Fig. 4A and B) and evoked stereotyped sniffing. The effects were approximately 8 times stronger after the injections into the GPa than those induced from the GPp. The enhancement of the locomotor activity induced by picrotoxin from the GPp was nevertheless dose-dependent. The injections of picrotoxin

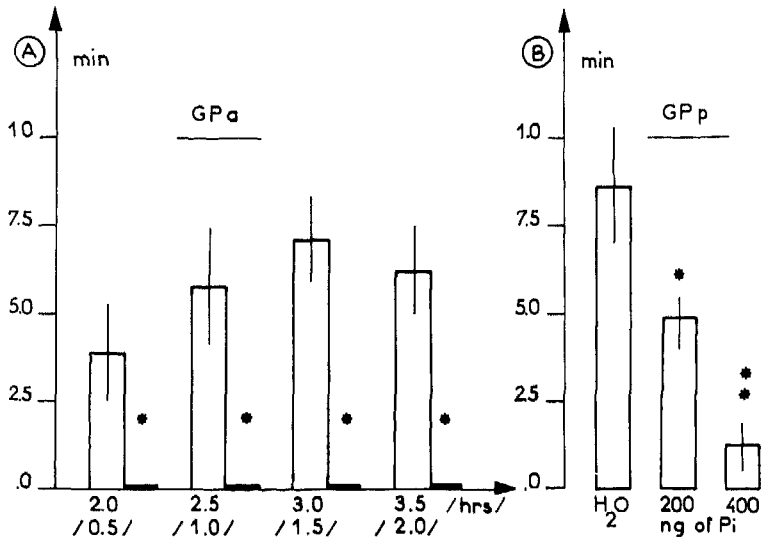

FIG. 6. The effects of bilateral injections of muscimol into the anterior part (GPa) and picrotoxin into the posterior part (GPp) of the globus pallidus on spiperone-induced catalepsy. Spiperone (0.2 mg/kg IP) was injected 1.5 hr before muscimol (200 ng/0.2 μl) or 2 hr before picrotoxin (Pi, 200 and 400 ng/0.2 μl/GPp). Catalepsy is expressed in minutes. A—open bars—combined treatment of solvent into the GPa and spiperone IP, black horizontal lines on the right of open bars—combined treatment of muscimol into the GPa and spiperone IP. Numbers in brackets—time in hours after injections of muscimol. Numbers without brackets—time in hours after injections of spiperone. B—open bars—combined treatment of solvent (H_2O) or picrotoxin (Pi) into the GPp and spiperone IP. The asterisk—significant difference to solvent treated rats at $p<0.05$ (Student's t-test).

into the GPp evoked occasionally stereotyped gnawing (Table 1).

The Influence of Picrotoxin and Bicuculline on Muscimol Effects

Muscimol catalepsy was blocked by bicuculline only while muscimol hyperactivity and stereotyped sniffing were abolished by the prior (30 min) intrapallidal injection of picrotoxin. Bicuculline inhibited the second phase of the muscimol effects only slightly (Fig. 5A and B).

In addition to the above described effects the combined injections of picrotoxin and muscimol or bicuculline and muscimol induced in numerous rats some epileptic phenomena, mainly body jerks (approximately 2 jerks/min). In some of the animals the combined bicuculline and muscimol injections produced even clonic-tonic convulsions.

The Effects of the Muscimol and Picrotoxin on the Spiperone Catalepsy and the Apomorphine-Induced Stereotypy

Muscimol (200 ng) injected bilaterally into the GPa 1.5 hr after an intraperitoneal administration of spiperone (0.2 mg/kg) abolished the spiperone catalepsy (Fig. 6A). Picrotoxin (200 and 400 ng) injected bilaterally into the GPp 2 hr after the intraperitoneal administration of spiperone (0.2 mg/kg) inhibited the spiperone catalepsy in a dose dependent manner (Fig. 6B). Muscimol (200 ng/GPa), which always produced stereotyped sniffing by itself, did not change the number of rats in which the stereotyped sniffing was observed after a combined injection with apomorphine (2.5 mg/kg SC); it abolished, however, the stereotyped licking and gnawing induced by apomorphine itself (Table 1). The rats which received the combined treatment with muscimol and apomorphine frequently stopped in an unnatural position, breaking sniffing and moving, as though petrified. However, if touched they reacted immediately and did not maintain any imposed unnatural position (catalepsy). In those rats an enhancement of the muscle tone, mainly within hind legs and marked balance disturbances were also observed.

Picrotoxin (400 ng/GPp) which induced stereotyped sniffing and gnawing by itself, did not change the amount of rats in which the stereotyped sniffing was observed after apomorphine (0.5, 1.0 and 2.5 mg/kg SC); it increased, however, the number of rats demonstrating gnawing and abolished stereotyped licking (Table 1).

DISCUSSION

The results presented indicate that the globus pallidus is a relay station for striatal impulses mediating neuroleptic catalepsy. It was shown that muscimol injected into the anterior and medial parts of the globus pallidus (GPa) evoked a neuroleptic-like catalepsy and then in the second stimulatory phase of its action blocked the catalepsy induced by spiperone. Muscimol injected into the posterior part of the globus pallidus (GPp) did not induce catalepsy but only diminished both the spontaneous locomotor activity and the hyperactivity induced by amphetamine. It might suggest that GPp is involved in the transmission of the impulses dealing only with the locomotor activity but not with the catalepsy. However, picrotoxin administered into the GPp decreased dose-dependently the catalepsy induced by spiperone. Hence, we conclude that GPp also mediates impulses in-

volved in the formations of the neuroleptic catalepsy. As the relationship between catalepsy and locomotor activity is not precisely determined (although many data support the supposition of different neuronal mechanisms mediating the phenomena), it cannot be excluded that the observed inhibition of spiperone catalepsy may be evoked by a mechanism primarily linked with the locomotor hyperactivity.

The conclusion suggesting participation of the globus pallidus in the formation of neuroleptic catalepsy is in line with the data obtained from experiments in which the structure was lesioned. It has been shown that bilateral electrolytic or kainic acid lesions of the globus pallidus provoke—until day 15 after lesioning—akinesia and strong catalepsy [22, 23, 29] while in the second recovery phase after the lesions (starting 3 weeks after lesioning) the neuroleptic catalepsy is blocked or at least strongly inhibited [3–5, 22]. In the second phase the rats were spontaneously hyperactive, unless treated with drugs. However, because of the very high mortality observed after the lesions both by Costall and co-workers and by us [3–5, 22] (40–80% of animals died within the first week after the lesion) it was not quite clear if in the first phase the animals were really cataleptic or simply ill. Therefore another experiment was needed to demonstrate the effects of inhibition of the globus pallidus in perfectly healthy rats. The results presented here fulfil this condition.

Moreover, it was demonstrated that the behavioural changes observed after injections of muscimol into the anterior and medial parts of the globus pallidus (GPa) resulted from the action of the drug on at least 2 different neuronal systems. One of them seems to be responsible for the first, cataleptic phase of the muscimol action while the other one may probably promote the second phase of hyperactivity noticed after the intrapallidal drug injection.

The hypothesis of 2 distinct neuronal systems is supported by divergence in the inhibitory effects of both GABA-antagonists, picrotoxin and bicuculline. The first counteracted the second phase of the muscimol action only, it means the hyperactivity induced by the drug. Bicuculline, on the contrary abolished the first cataleptic phase of muscimol action. As the actions of muscimol and bicuculline are restricted to the $GABA_A$ receptor and the effect of picrotoxin also seems to be linked in the GABA receptor complex, no hypotheses can be advanced on the participation of $GABA_B$ receptor in the observed effects. It seems most probable that either of the GABA-lytics blocked the action of muscimol on a different neuronal target, as the extent to which each substance spreads within the 2 hr of the muscimol action may be different. Although bicuculline methiodide is more stable in plasma than is bicuculline base, we know nothing about its lifetime in the brain. It is, however, well known that its action on the animal behaviour is much shorter than that of muscimol and picrotoxin. Moreover, since bicuculline is a quaternary ammonium compound, its diffusion may be more restricted than that of muscimol or picrotoxin.

It is somewhat puzzling that effects of picrotoxin seemed to be uniform and that no second phase of the drug action could be distinguished. Admittedly, it is well known that a direct effect of an antagonist is usually more difficult to detect than that of an agonist. The action of an antagonist is usually demonstrated indirectly, through its inhibitory activity directed against the effects of an agonist. In fact the second phase of the picrotoxin action may be detected but only through the blockade of the muscimol-evoked hyperactivity (Fig. 5) which started exactly 90 min after picrotoxin injection, i.e., just at the time when the first stimulatory phase of the picrotoxin action on the locomotor activity disappeared (Fig. 4). Thus picrotoxin actually acts biphasically but the second phase of its action is only more difficult to detect.

The appearance of the second phase of the action of both drugs was markedly delayed, by approximately 60 min for muscimol and by 90 min for picrotoxin. It may suggest that the second neuronal system which is responsible for the second phase of their effects is in fact located more distant from the injection site than that one which promotes the first cataleptic phase. It may even be speculated that it is located out of the globus pallidus. Our unpublished results of the injections of muscimol and picrotoxin into the substantia innominata of rabbits, just below the globus pallidus, as well as those obtained by Scheel-Krüger (personal communication) on rats, seem to point out this structure as a possible place where the second phase of muscimol and picrotoxin actions could have their target points.

Our results substantially confirm and extend those reported by Scheel-Krüger and co-workers [25,26], but they are at variance with the results of Moroni *et al.* [20], Matsui and Kamioka [16] and Di Chiara *et al.* [6]. Di Chiara *et al.* [6] reported that after the injection of up to 50 ng of muscimol into the globus pallidus no catalepsy was observed. However, the catalepsy caused by such a dose is in fact relatively weak. On the other hand Moroni *et al.* [20] described a strong and long-lasting (up to 3 hr) catalepsy after injections of approximately up to 170 ng of muscimol into the globus pallidus of rats. However, the drug was injected in a relatively high volume of 1 μl (while we injected only 0.2 μl), and the authors themselves noticed that muscimol could act perhaps on some neighboring structures. In fact muscimol (50 ng) injected into the adjacent nucleus reticularis thalami of rats evokes strong and long-lasting catalepsy (Wolfarth *et al.*, unpublished data). Matsui and Kamioka [16] after the intrapallidal injection of muscimol observed the catalepsy only. It seems they might not be interested in any other results.

The stereotyped behaviour induced by apomorphine seems also to be mediated by the globus pallidus. The fact that muscimol and picrotoxin injected into the GPa induce, in different phases of its action, stereotyped sniffing and that picrotoxin administered into the GPp provokes sniffing and gnawing supports this hypothesis. These components of the stereotyped behaviour might be mediated either by GP itself or by GP and adjacent structures. Furthermore, the blockade of the stereotyped licking induced by apomorphine also suggests that this component of the stereotyped behaviour might be transmitted by GP. All these results are in line with the effect of systemic injections of apomorphine and picrotoxin which increased the firing rate of globus pallidus neurons while muscimol decreased it [1,27]. However, although the GABAergic mechanisms of the GP are certainly involved in the mediation of the stereotyped behaviour a separate study is necessary to elucidate the precise mechanisms which are responsible for these phenomena.

ACKNOWLEDGEMENTS

We are grateful to Dr. A. Wauquier from Janssen Pharmaceutica and to Dr. A. V. Christensen from H. Lundbeck Co. for the generous gifts of spiperone and THIP respectively.

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