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Potentiation by Neuroleptic Agents of the Inhibitory Action of Intraperitoneally Administered GABA on the Locomotor Activity of Mice

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BISWAS, B. AND A. CARLSSON. *Potentiation by neuroleptic agents of the inhibitory action of intraperitoneally administered GABA on the locomotor activity of mice.* PHARMAC. BIOCHEM. BEHAV. 8(6) 651–654, 1978. – The ability of several neuroleptics to potentiate the inhibitory action of IP administered GABA on the motor activity of mice has been investigated. Haloperidol, chlorpromazine, thioridazine, and clozapine, but not the apparently selective dopamine receptor-blocking agent spiperone, were found to possess such activity. Phenoxybenzamine also proved active in potentiating GABA. Thus blockade of dopamine receptors as well as α-adrenergic receptors may be responsible for neuroleptic-induced potentiation of GABA actions.

Neuroleptics GABA Locomotor activity

IN PREVIOUS communications we have presented evidence that systemically administered GABA is capable of influencing central monoaminergic mechanisms and of exerting a central depressant action [2,3]. The pattern of activity was similar to that observed after intracerebroventricular administration of GABA [4], thus supporting the hypothesis that GABA is capable of reaching at least certain central neurons from the blood stream.

In otherwise untreated animals the IP dose of the GABA required for inhibiting motor activity to a significant degree was rather high, i.e., 2000 mg/kg. However, a considerable increase in the sensitivity to GABA was brought about by pretreatment with ethanol or haloperidol, where IP GABA proved active in doses down to 100 mg/kg after such pretreatment.

In agreement with these observations Kääriäinen [6] reported that amino-oxyacetic acid, an inhibitor of GABA transaminase, and baclophen, a GABA derivative, are capable of potentating the cataleptic action of haloperidol.

In the present communication the ability of haloperidol and several other neuroleptic agents to potentiate the action of IP administered GABA is further investigated.

METHOD

Female mice weighing about 20 g of the NMRI strain were used. The following drugs were administered: Haloperidol (Haldol®, AB Leo*, Helsingborg, Sweden), spiperone (Janssen*, Beerse, Belgium), clozapine (Wander*, Bern), chlorpromazine HCl (Hibernal®, AB Leo*, Helsingborg, Sweden), thioridazine HCl (Mallorol®, Sandoz*, Basle, Switzerland), phenoxybenzamine HCl (AB Leo*, Helsingborg, Sweden) and gamma-aminobutyric acid (GABA, Sigma).

Locomotor activity was measured using the "M/P 40 Fc Electronic Motility Meter" (Motron Products, Stockholm) [1]. Every tenth interruption of the photocell beam was counted. The animals in groups of three were placed in each activity box and cumulative counts for 20 min were recorded.

Thioridazine (0.5 mg/kg), clozapine (1.0 mg/kg) and chlorpromazine (0.3 mg/kg) were injected alone or in combination with GABA (100 mg/kg). Spiperone was injected at different doses (0.01 to 0.15 mg/kg) in combination with the same dose of GABA. Different doses of haloperidol (0.025 to 0.15 mg/kg) were injected, either alone or in combination with different intraperitoneal doses of GABA (5 to 250 mg/kg). All neuroleptics were given before the injection of GABA or corresponding saline. (The exact time of injection has been mentioned in the RESULT section.) Recording locomotor activity was started about 1 min after the injection of GABA. Phenoxybenzamine (0.5 mg/kg and 0.75 mg/kg) was given 1 hr prior to GABA injection.

Statistics

Statistical calculations were done by one-way analysis of variance followed by Student's *t* test.

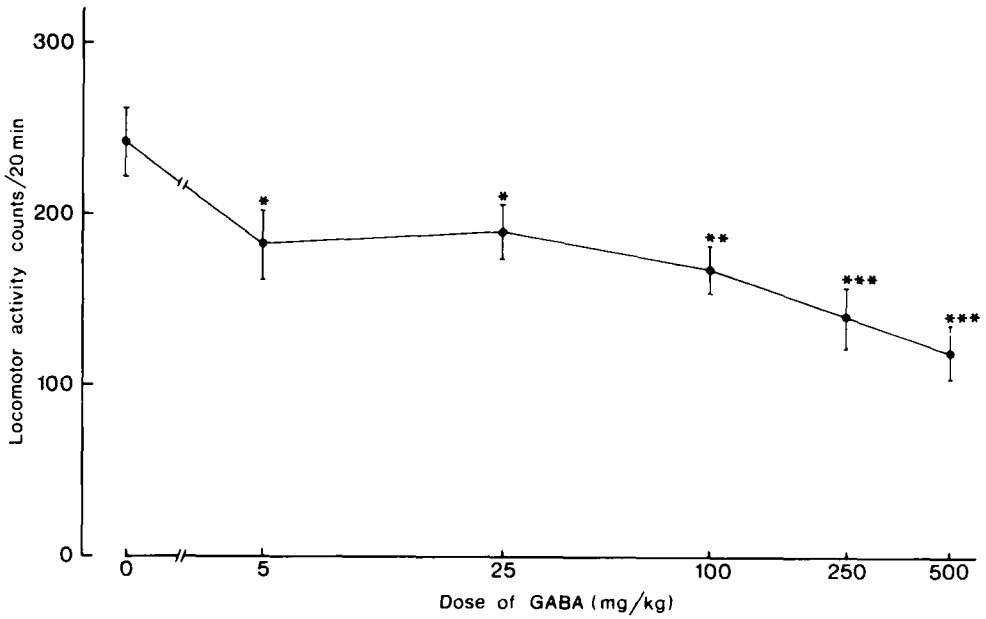

FIG. 1. Effect of various doses of GABA (given IP 1 min before recording) on the locomotor activity of mice, pretreated with haloperidol (0.15 mg/kg IP, 20 min before recording

RESULTS

The dose-response curve of IP administered GABA in mice pretreated with a fixed dose of haloperidol (0.15 mg/kg) is shown in Fig. 1. Doses down to 5 mg/kg proved active in inhibiting motility. A certain further inhibition was observed after higher doses of IP GABA.

If the pretreatment dose of haloperidol was reduced from 0.15 to 0.05 mg/kg, a dose still active per se, GABA, 100 mg/kg IP, produced but a slight, statistically not significant decrease in motility (Table 1).

Haloperidol appears to be a rather selective dopamine-receptor blocking agent. It appears to be capable of blocking also α-adrenergic receptors although larger doses are required [5]. Spiperone appears to be an even more selective dopamine-receptor blocking agent. However, this agent appeared to be unable to potentiate the action of IP GABA (Table 2).

A number of neuroleptics with lower selectivity as regards blockade of dopamine receptors, i.e., chlorpromazine, thioridazine and clozapine, were also investigated. When given in doses which per se were inactive (thioridazine and chlorpromazine) or moderately active (clozapine), they were all found to potentiate the action of IP GABA (Table 3).

Since the neuroleptics studied in Table 3 appear to block not only dopamine receptors but also α-adrenergic receptors [5], the effect of phenoxybenzamine, a potent α-adrenergic receptor-blocking agent, was also investigated. When given in an IP dose of 0.75 but not 0.5 mg/kg, it proved active in potentiating the action of IP GABA (Table 4). A

TABLE 1

EFFECT OF HALOPERIDOL AND GABA ON THE LOCOMOTOR ACTIVITY OF MICE

Treatment	Dose (mg/kg)	Locomotor Activity (counts/20 min) Drug + Saline (a)	Drug + GABA (b)	p (a) vs. (b)
Saline		461 ± 15 (16)	444 ± 41 (5)	>0.05
Haloperidol	0.05	331 ± 31* (8)	285 ± 9 (7)	>0.05
	0.15	242 ± 22 (9)	169 ± 15 (6)	<0.05

Variance within groups = 4168. Shown are the means ± SEM. Figures in parentheses indicate number of experimental groups, each comprising three animals.

*$p<0.001$ vs. saline. Haloperidol was given 20 min and GABA (100 mg/kg IP) 1 min before measuring the locomotor activity.

TABLE 2

EFFECT OF VARIOUS DOSES OF SPIPERONE ALONE OR IN COMBINATION WITH GABA ON THE LOCOMOTOR ACTIVITY OF MICE

Treatment	Dose (mg/kg)	Locomotor Activity (counts/20 min) Drug + Saline	Drug + GABA
Saline		461* ± 15 (16)	444 ± 41 (5)
Spiperone	0.01	362 ± 16 (7)	327 ± 33 (5)
	0.02	320 ± 29 (5)	322 ± 23 (5)
	0.03	387 ± 34 (6)	322 ± 40 (6)
	0.06	373 ± 30 (4)	357 ± 42 (5)
	0.10	244 ± 18 (4)	245 ± 17 (4)
	0.15	151 ± 10 (4)	170 ± 23 (4)

Variance within groups = 4079. Shown are the means ± SEM. Figures in parentheses indicate number of experimental groups, each comprising three animals.

*Differs from all spiperone-treated groups ($p<0.005$). Spiperone-treated groups vs. spiperone + GABA is always $p>0.05$. Spiperone was given 20 min and GABA (100 mg/kg IP) 1 min before measuring the locomotor activity.

TABLE 3

EFFECT OF DIFFERENT NEUROLEPTICS ALONE OR IN COMBINATION WITH GABA ON THE LOCOMOTOR ACTIVITY OF MICE

Treatment	Dose (mg/kg)	Locomotor Activity (counts/20 min) Drug + Saline (a)	Drug + GABA (b)	p (a) vs. (b)
Saline	–	461 ± 15 (16)	444 ± 41 (5)	>0.05
Thioridazine	0.5	464 ± 38 (8)	313 ± 21 (9)	<0.001
Clozapine	1.0	340* ± 19 (8)	254 ± 14 (5)	<0.05
Chlorpromazine	0.3	440 ± 20 (6)	327 ± 17 (6)	<0.01

Variance within groups = 4564. Shown are the means ± SEM. Figures in parentheses indicate number of experimental groups, each comprising three animals.

*$p<0.001$ vs. saline. Thioridazine and clozapine were given 20 min and chlorpromazine 1 min before GABA. Locomotor activity was recorded 1 min after GABA (100 mg/kg, IP) injection.

combination of phenoxybenzamine, 0.75 mg/kg, with spiperone 0.06 mg/kg, appeared no more potent than phenoxybenzamine alone in potentiating the action of IP GABA.

DISCUSSION

The present investigation has shown that a number of neuroleptic agents are capable of potentiating the inhibitory action of IP administered GABA on the motility of mice. However, spiperone, an agent supposed to be highly selective in blocking dopamine receptors, proved inactive in this regard. On the other hand phenoxybenzamine, a selective α-adrenergic receptor-blocking agent, proved active. The question may thus be raised whether the α-adrenergic receptor-blocking activity, which many neuroleptics have in common, although this activity is generally less pronounced than the dopamine receptor-blocking action, might be responsible for potentiation of GABA. It should be recalled that GABA appears to stimulate noradrenergic neurons [2]. It does not seem unreasonable to assume that this stimulation serves to counteract the inhibitory action of GABA on locomotion. The present data

TABLE 4

EFFECT OF SPIPERONE, GABA AND PHENOXYBENZAMINE (PBZ) ON THE LOCOMOTOR ACTIVITY OF MICE

Treatment	Dose (mg/kg)	Locomotor Activity (counts/20 min) Drug + Saline (a)	Drug + GABA (b)	p (a) vs. (b)
Saline	–	461 ± 15 (16)	444 ± 41 (5)	>0.05
PBZ	0.5	390* ± 38 (6)	370 ± 11 (6)	>0.05
	0.75	416 ± 32 (6)	261 ± 20 (6)	<0.001
Spiperone	0.06	436 ± 14 (5)	385 ± 21 (5)	>0.05
PBZ	0.75			
+	+	433 ± 33 (6)	294 ± 39 (6)	<0.001
Spiperone	0.06			

Variance within groups = 4723. Shown are the means ± SEM. Figures in parentheses indicate number of experimental groups, each comprising three animals.

*$p<0.05$ vs. saline. PBZ was given 60 min and spiperone 1 min before GABA. Locomotor activity was measured 1 min after GABA (100 mg/kg IP) injection.

do not contradict this possibility, even though some other as yet unidentified action of the neuroleptics investigated may be responsible for their ability to potentiate systemically administered GABA. Moreover, it may be mentioned in this connection that different neuroleptics have been claimed to affect brain GABA systems differentially [7]. An alternative interpretation of the present observation is that neuroleptics in general are capable of potentiating IP GABA by means of their dopamine receptor-blocking properties, to which α-adrenergic blockade may contribute. The exceptional behaviour of spiperone would then be due to some unidentified property of this agent, which would serve to neutralize the GABA potentiation induced by dopamine-receptor blockade.

In any event the observations made in this investigation emphasize the heterogeneity of the neuroleptic drugs, whose profile of activity is probably determined by several sites of action, in addition to blockade of dopamine receptors. This heterogeneity must be kept in mind in future investigations on the interaction between neuroleptics and GABA-ergic drugs.

In this discussion the action of GABA has been stated to be potentiated by neuroleptic drugs. The question may be raised whether it would not be preferable to state that the action of neuroleptics is potentiated by GABA. Since both agents per se, when given in sufficiently large doses, have an inhibitory action on motility [3] we feel that both ways of stating the relationship are acceptable and that the question, as to which way is preferable, is largely academic.

Very large intraperitoneal doses of GABA (25 mmoles/kg) given in hyperosmotic solution, have been shown to cause dehydration of the brain and to protect against convulsions [8]. The dosage of GABA used in our study are about two orders of magnitude lower, and thus dehydration of the brain is probably not an important factor for the activity described in the present paper.

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