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Interaction Between Phencyclidine (PCP) and Gaba-ergic Drugs: Clinical Implications

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MENON, M. K., W. G. CLARK AND C. VIVONIA. *Interaction between phencyclidine (PCP) and gaba-ergic drugs: Clinical implications*. PHARMAC. BIOCHEM. BEHAV. 12(1) 113–117, 1980.—Pretreatment (IP) of mice with (−) baclofen, muscimol, 4,5,6,7-tetrahydroisoxazolo (S,4-c) pyridin-3-ol hydrate (THIP), aminooxyacetic acid (AOAA) or γ-acetylenic GABA caused a dose-dependent inhibition of the locomotor stimulant effect of phencyclidine (PCP, 8 mg/kg). Although (−) baclofen was found to be the most effective PCP antagonist, its (+) isomer was inactive. The maximum blocking effect of AOAA was seen in animals treated 3 and 6 hr earlier. Except for γ-acetylenic GABA, none of these drugs significantly blocked the locomotor stimulant effect of d-amphetamine (3 mg/kg, IP). Diazepam reduced d-amphetamine response, but failed to influence PCP-induced stimulation. The locomotor stimulant effect of PCP, unlike that of d-amphetamine, may be the result of a specific GABA antagonistic effect at certain dopamine-rich areas of the brain. It seems that (−) baclofen may prove to be useful in the management of PCP intoxication.

Administration of higher doses of PCP (20 and 50 mg/kg) in mice pretreated with (−) baclofen resulted in the development of surgical anesthesia manifested as the loss of a) righting reflex, b) pain sensation and c) corneal reflex. The duration of the general anesthetic response was found to be a function of the doses of both (−) baclofen and PCP. The possible use of (−) baclofen as an adjuvant to general anesthetic is discussed.

Phencyclidine d-Amphetamine Baclofen Muscimol Aminooxyacetic acid γ-Acetylenic GABA Locomotor stimulation Surgical anesthesia

AS a result of the serious psychiatric disturbances it causes in humans, phencyclidine (PCP) which was introduced in 1958 as a general anesthetic agent enjoyed only a brief clinical usage [9]. Renewed interest in this drug stems from its widespread abuse. Known among the drug abusers as "angel dust", PCP produces a variety of psychiatric symptoms characterized by disorientation, schizophrenia-like psychosis, uncontrolled violent reactions and convulsions [23, 24, 26, 27, 33]. Presently the treatment of PCP intoxication is rather empirical, diazepam being commonly used in the management of anxiety reactions and convulsions. Our recent observation that baclofen (Lioresal) blocks the behavioral effects of PCP in mice and rats prompted us to propose its use in the clinical management of phencyclidine intoxication [25]. In the present communication, details of the interaction of PCP with baclofen as well as with other drugs which enhance the activity of the gamma aminobutyric acid (GABA) system are reported.

METHOD

Male Swiss mice (23–28 g) obtained from Hilltop Laboratories, Scottdale, PA were used and the experiments were performed at a room temperature of 23 ± 1°C. The drugs used in these studies were phencyclidine HCl (Phillips Roxane, Inc., St. Joseph, MO); d-amphetamine sulfate (Smith, Kline and French Labs., Philadelphia, PA); (±) baclofen HCl (Lioresal, Ciba-Geigy, Summit, NJ); (+) and (−) baclofen HCl (Ciba-Geigy, Basel, Switzerland); muscimol HBr, 4,5,6,7-tetrahydroisoxazolo (S,4-c) pyridin-3-ol hydrate (THIP) (from Dr. P. Krogsgaard-Larsen Copenhagen); aminooxyacetic acid (Upjohn Co., Kalamazoo, MI); diazepam (Hoffman-La Roche, Nutley, NJ); and γ-acetylenic GABA (Merrell International, Strasbourg, France). Diazepam was dissolved in 0.1 N HCl and diluted with distilled water. All the other drugs were dissolved in distilled water. The drug solutions were administered intraperitoneally (IP) in a volume of 0.01 ml per gm body weight of the animal. Of the doses mentioned, only that of PCP and d-amphetamine represent the free base.

Locomotor Activity

The animals were placed individually in transparent plastic cages (containing a thin layer of wood shavings) on an activity meter (Varimex, Columbus Instruments, OH). At the end of a one-hour familiarization period, different groups were pretreated with distilled water or with various drugs, namely (±) baclofen (10 min prior), baclofen isomers (10 min prior), muscimol HBr (10 min prior), THIP (15 min prior) or diazepam (10 min prior). Mice receiving AOAA (1, 3, 6 and 8

[1]Deceased 2-13-79.

hr prior) or γ-acetylenic GABA (4 hr prior) were permitted the 1 hr familiarization period after these treatments.

The pretreated mice received either PCP (8 mg/kg base) or d-amphetamine sulfate (3 mg/kg base). The activity meter was started immediately and the readings were recorded on a print-out counter (Columbus Instruments, OH). Earlier studies showed that these doses of PCP and d-amphetamine produce submaximal locomotor stimulation in mice, the maximal effect being over at 60 min.

Influence of (−) Baclofen on the Behavioral Responses of High Doses of PCP

During our interaction studies of PCP with (±) baclofen, we observed that combined treatment of higher doses of these drugs resulted in the loss of righting reflex. Hence, we performed detailed studies to determine the dose levels of the active form of (±) baclofen, namely the (−) isomer necessary to produce a general anesthetic response in mice receiving a subsequent injection of a lower dose (20 mg/kg) or a higher dose (50 mg/kg) of PCP. For this purpose, the animals were pretreated with (−) baclofen and 10 min later PCP was administered. They were placed in individual chambers and the following observations were made: (1) the elapsed time between the loss and the subsequent regaining of the righting reflex (sleeping-time), (2) the duration of loss of pain sensation (analgesic response). Response to pain was tested by applying mechanical compression to the tail at intervals, no attempt being made to quantitate the degree of the response. (3) Duration of the loss of corneal reflex, and (4) lethality within 8 hr.

RESULTS

Locomotor Activity

The locomotor stimulant effects of both PCP and d-amphetamine were evident within 5 min after administration and the maximum effects were over by 60 min. Their responses were characterized by compulsive running activity. Mice pretreated with (±) baclofen, (−) baclofen, muscimol, THIP hydrate and diazepam showed a dose-dependent decrease in locomotor activity. In higher doses, animals receiving these drugs showed moderate muscle relaxation. Such effects were also observed 3 hr after the treatment with γ-acetylenic GABA or AOAA. In the AOAA treated mice, these effects persisted for 6 hr, but the animals became active at 8 hr. Even in a dose of 20 mg/kg, (+) baclofen did not induce behavioral changes in mice.

Mice pretreated with (±) baclofen failed to show locomotor stimulation when challenged with PCP and its effect was found to reside in the (−) isomer (Table 1). Though the depressant effects in mice seen after (−) baclofen (5 mg/kg) were roughly equal to those of muscimol (1.5 mg/kg) or THIP hydrate (5 mg/kg), as PCP antagonists these drugs were weaker than (−) baclofen. γ-Acetylenic GABA significantly blocked PCP response, but was weaker than AOAA in this regard. The blocking effect of AOAA was maximum in the 3- and 6-hr pretreatment groups (Table 1). Diazepam did not block the PCP response. Only the diazepam and γ-acetylenic GABA pretreated groups showed significant blockade of d-amphetamine-induced stimulation.

Interaction Between (−) Baclofen and Higher Doses of PCP

The results are given in Table 2. PCP, even in a dose of 50 mg/kg failed to produce either a loss of righting reflex or analgesic response in mice. Loss of pain sensation was seen in mice receiving (−) baclofen, a minimum dose of 20 mg/kg being required for the manifestation of this response. In a dose of 50 mg/kg, loss of righting reflex, lasting for about 60 min was seen in about 90 percent of the animals receiving (−) baclofen.

Combined administration of adequate doses of these two drugs resulted in the development of surgical anesthesia characterized by the abolition of righting reflex, pain sensation and corneal reflex (Table 2). The minimum pretreatment dose of (−) baclofen to produce surgical anesthesia on administration of a subsequent dose of 20 mg/kg PCP was found to be 20 mg/kg. On increasing the dose of (−) baclofen, a dose-dependent enhancement in the sleeping time was observed with more or less parallel increases in the duration of both analgesia and the loss of corneal reflex. When the dose of PCP was increased to 50 mg/kg, (−) baclofen pretreatment resulted in the further intensification of all the three responses. Up to a certain dose level, parallel increases in lethality were not observed. However, a combination of 50 mg/kg each of (−) baclofen and PCP produced death in more than 50 percent of the animals.

DISCUSSION

The locomotor stimulant effect of PCP in mice and rats was first reported in 1959 [5]. More recent studies indicate that the central stimulant effect of PCP involves the activation of the dopaminergic system. Thus, like other dopaminergic drugs, PCP induces stereotyped behavior in rats [2], guinea pigs [15], monkeys [32], and humans [4]. Moreover, PCP causes ipsilateral rotation in rats with unilateral nigrostriatal lesions, this effect being antagonized by α-methyl-p-tyrosine (α-MT), haloperidol and pimozide [11,17]. The influence of PCP on the metabolism of brain dopamine (DA) has also been determined. PCP significantly decreases the depletion of brain DA by α-MT [22] and has also been found to be a potent competitive inhibitor of dopamine uptake in rat corpus striatum [13,34].

Although all of the above effects of PCP clearly indicate its close similarity with d-amphetamine, the present results show that the mechanism by which PCP exerts locomotor stimulation in mice differs from that of d-amphetamine. The putative GABA receptor agonists baclofen [1, 8, 12]; muscimol [3, 29, 35]; THIP [19,20] as well as the GABA-elevating drugs such as AOAA [21,39] and γ-acetylenic GABA [16,31] significantly inhibited the locomotor stimulant effects of PCP. In the AOAA pretreated mice, maximal blocking effect was seen at 3 and 6 hr, times at which maximal brain GABA elevation is known to occur [21,39]. Except for γ-acetylenic GABA, none of the other drugs significantly blocked the response of d-amphetamine. Thus, it seems that the PCP-induced locomotor stimulation involves the GABA-ergic system unlike the locomotor stimulation of d-amphetamine.

Several neuroanatomical, electrophysiological and biochemical studies have demonstrated the interrelationship between the central DA and GABA systems, and it is now believed that the descending pathway between the neostriatum and the substantia nigra is mediated by GABA and exerts an inhibitory influence on the substantia nigra neurons [28]. Hence, theoretically, a procedure which interferes with the inhibitory effect of the GABA-ergic system would result

TABLE 1

EFFECTS OF GABA-ERGIC DRUGS ON THE LOCOMOTOR STIMULATION PRODUCED IN MICE BY PHENCYCLIDINE OR D-AMPHETAMINE*

Pretreatment†	60 min activity ± SE produced by: Phencyclidine 8 mg/kg	Probability‡	d-amphetamine 3 mg/kg	Probability‡
Distilled water (control)	2091 ± 235		1595 ± 247	
(±) baclofen				
5.0	618 ± 187	<0.001		
10.0	61 ± 17	<0.001	1646 ± 241	N.S.
(−) baclofen				
1.0	1862 ± 211	N.S.		
3.0	979 ± 131	<0.001		
5.0	43 ± 19	<0.001		
(+) baclofen				
5.0	2734 ± 110	<0.05		
20.0	2681 ± 270	N.S.		
Muscimol HBr				
0.75	1488 ± 422	N.S.		
1.5	474 ± 223	<0.001	1516 ± 131	N.S.
THIP hydrate				
3.0	1845 ± 182	N.S.	1537 ± 188	N.S.
5.0	984 ± 201	<0.01	1173 ± 182	N.S.
γ-acetylenic GABA				
100.0	714 ± 125	<0.001	773 ± 151	<0.025
Diazepam				
3.0	1549 ± 329	N.S.	954 ± 190	<0.05
AOAA 50				
1 hr	327 ± 127	<0.001		
3 hr	147 ± 56	<0.001	1568 ± 132	N.S.
6 hr	183 ± 157	<0.001		
8 hr	1142 ± 168	<0.01		

*N=8–12 in each group. The 60 min locomotor activity of mice not receiving either PCP or d-amphetamine was 460 ± 88 (N=12).

†For schedule see Methods.

‡Probability was caluculated using Student's *t*-test. Comparisons were made with the respective control groups.

in responses indicative of dopaminergic hyperactivity. Thus, it has been found that intrastriatal injections of picrotoxin, a postsynaptic GABA antagonist, produced contralateral rotational behavior in rats with intact nigral pathways [36]. Conversely, unilateral focal elevation of GABA in the substantia nigra [10, 14, 18] or the intranigral application of either baclofen or muscimol [37] results in spontaneous or drug-induced rotation. These latter effects are presumed to be the consequence of feedback hypoactivity of the dopaminergic areas of the injected side. Based on these findings it seems possible that the PCP-induced locomotor stimulation in mice is related to the GABA-antagonistic effect of this drug on specific sites of the brain, the striatonigral and mesolimbic dopaminergic areas being the most likely ones involved. Both electrophysiological and biochemical studies have to be performed to substantiate the proposed mode of action of PCP. At this point, it may be necessary to emphasize the fact that the GABA-antagonistic effect of PCP leading to dopaminergic hyperactivity represents only one (perhaps a major) aspect of its mode of action. Though in the present study, emphasis has been placed on this aspect, the contribution of other neurotransmitter systems such as norepinephrine and serotonin (for references see [17]) to the full manifestation of psychiatric symptoms by PCP cannot be ignored.

Of all the drugs tested, baclofen produced the most impressive results. Its activity was found to reside in the (–) isomer. The stereospecificity of baclofen has been demonstrated by other investigators also [30,38]. Although many consider baclofen to be a GABA agonist (for references see above), its specificity has been questioned by others [7,29]. The more complete blockade of PCP stimulation by (−) baclofen seems to imply that properties of this compound other than its GABA agonist effect might have contributed to its PCP antagonism. Whatever the mechanism involved in this interaction, it appears that (−) baclofen could be potentially

TABLE 2

POTENTIATION OF THE CENTRAL DEPRESSANT EFFECTS OF PHENCYCLIDINE BY (−) BACLOFEN

Treatment (dose mg/kg)	No. mice	Sleeping time (min ± SE)	Duration of analgesia* (range in min)	Duration of loss of corneal reflex*	Death in 8 hrs†
Phencyclidine (PCP)					
50	5	0	0	0	0
(−) Baclofen					
10	5	0	0	0	0
20	5	0	23– 25 (5)	0	0
30	5	0	71– 80 (5)	0	0
50	9	62 ± 10 (8)	81– 84 (5)	0	1 (85 min)
(−) Baclofen + PCP					
10 + 20	6	91 ± 6 (6)	0– 50 (3)	0	0
20 + 20	6	126 ± 30 (5)	42– 64 (5)	7– 30 (5)	0
30 + 20	6	183 ± 12 (6)	53–205 (6)	11– 48 (6)	1 (206 min)
50 + 20	6	260 ± 42 (6)	84–154 (6)	139–162 (6)	0
20 + 30	6	182 ± 5 (6)	84–195 (6)	130–135 (6)	0
10 + 50	17	222 ± 12 (16)	45– 72 (4)	43–106 (5)	1 (14 min)
20 + 50	13	298 ± 13 (12)	81–132 (6)	78–400 (12)	1 (15 min)
30 + 50	13	310 ± 17 (12)	33–240 (12)	91–260 (12)	1 (224 min)
50 + 50	13	351 ± 18 (6)	181–282 (6)	178–270 (6)	7 (9–360 min)

*The values represent the responses of those animals in the group which showed the particular effect, the numbers of which are given in parentheses.

†The numbers in parentheses indicate the time at which the animals died.

useful in the management of PCP intoxication. In this regard it is interesting to note that, when administered after PCP, baclofen is capable of reversing a fully-developed motor excitation in mice and rats caused by the former [25].

Combined administration of higher doses of PCP and (−) baclofen resulted in the production of surgical anesthesia. Although PCP itself is known to exert similar responses in rhesus monkeys and humans, such responses are not produced in rodents even by high doses of PCP [5, 6, 9]. This anesthesia-induced property of (−) baclofen may also have clinical significance especially if it could be shown that baclofen abolishes the post-operative hallucinogenic sequelae seen after PCP. Our recent studies also indicated that (−) baclofen potentiates the general anesthetic effect of both pentobarbitone and of ketamine (to be published). The present studies demonstrating the potentiation of the central depressant effect of PCP by (−) baclofen may also form a helpful guideline for determining the therapeutic dosage of baclofen during its clinical trial as an antagonist of PCP.

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