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Behavioral Effects Induced by Beta CCE in Free or Restrained Rhesus Monkeys *(Macaca mulatta)*

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LAGARDE, D., J. LAURENT, C. MILHAUD, E. ANDRE, H. J. AUBIN AND G. ANTON. *Behavioral effects induced by beta CCE in free or restrained rhesus monkeys* (Macaca mulatta). PHARMACOL BIOCHEM BEHAV **35**(3) 713–719, 1990.—Behavioral effects of the IV injection of beta carboline carboxylic acid ethyl ester (beta CCE) were studied in chair-restrained rhesus monkeys and in rhesus monkeys freely moving in their cages. Observations made during the administration of increasing doses of beta CCE (0.5, 1 and 2 mg/kg) evidence behaviors reflecting a state of anxiety. The similarity of results obtained under the two experimental conditions excludes a potential effect of restraint on the behavioral expression of effects induced by the administered molecule. Convulsions observed in three subjects out of twelve should call for great caution when using this molecule.

Beta carboline carboxylic acid ethyl ester (BCCE) Free rhesus monkeys Restrained rhesus monkeys Behavior Anxiety model Convulsive crises

BCCE (beta carboline carboxylic acid ethyl ester) is considered as an inverse agonist of benzodiazepine receptors (16). It is capable of expelling ^{3}H-diazepam from its specific binding site (12,23) and its convulsion inducing, stimulating, anxiogenic and promnesiant properties were evidenced, especially in rodents (2, 3, 9, 17, 22).

Anxiogenic properties of BCCE could be used to test, by inhibition of this type of effect, the specifically anxiety relieving properties of new substances. This investigation was designed to gain better knowledge of the anxiogenic effects of BCCE in the rhesus monkey animal model. Because of its phylogenetic closeness to man, the similarity of its metabolic pathways and its varied behavior, the rhesus model should permit rapid and reliable transfer to man of data regarding the inhibition of anxiogenic crisis by new anxiety relieving substances (4, 9, 10, 14, 16).

The study of the anxiogenic crisis reported both in restrained (4,16) or caged (9) rhesus monkeys after administration of BCCE yields very inconsistent results. It seems, therefore, indispensable to study again the effects of BCCE on rhesus monkeys using a common protocol, comparing effects observed in restrained subjects with those observed in caged subjects.

METHOD

Animals

Experience 1 (chair restraint). Four adult rhesus monkeys (about 8–10 kg body weight) were used. These animals were thoroughly adapted to laboratory conditions, and especially to restraint in a chair specially designed to allow the animal to sleep in a position close to its physiological position (15).

From a pharmacological standpoint, subjects had not received any psychotropic drugs for at least five weeks prior to the experiment.

Experience 2 (no restraint). Eight adult rhesus monkeys (about 4–6 kg body weight) were used. These animals were used to living in the same room. They were kept in individual cages (120 × 80 × 50 cm) equipped with automatic waterers.

Facilities

Experiment 1. Animals in their restraint chairs were placed in groups of two, side by side, on a platform. They could see and touch each other. Each group was placed in a sound-proof, ventilated and lit isolation chamber. Animals were observed on a

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video monitor and their behavior was recorded using a camera and a video recorder.

Experiment 2. Animals were placed in two cages identical to maintenance cages and their behavior was recorded by a video system.

Substances

Doses of 0.5, 1 and 2 mg/kg beta-carboline carboxylic acid ethyl ester (Research Biochemicals Inc.) in a volume of 0.1 ml/kg were administered intravenously (external saphenous vein). The compound was dissolved in an acidic medium in a PBS pH 7.4 buffer.

Experimental Procedure 1

Animals were observed by pairs. Each subject received the four treatments: placebo, 0.5, 1 and 2 mg/kg BCCE, administered in a random order (Latin square distribution).

The molecule or placebo were administered at time T. The double-blind behavioral observation immediately started after administration to each animal and lasted for one hour. Behavioral criteria were recorded off-line using a behavioral scale defined according to studies done by Ninan (16), Crawley (4), Altmann (1) and Redmond (18) in restrained monkeys as well as using our own experience gained in the laboratory.

Duration and frequency of behaviors were recorded using a portable digital acquisition system (DATAMYTE 1000).

Seven behaviors were defined:

1. Calm: behavior excluding behavioral sleep and agitation.
2. Behavioral sleep: motionless with closed lids and hypnotic appearance.
3. Agitation: the quantity and vivacity of motions exceeds a threshold subjectively defined by the observer as a function of his experience of animal behavior; motions usually have no apparent purpose and are not the support of a behavior.
4. Aggressiveness: behavior mostly directed toward the neighboring monkey.
5. Staring: eyes are open, looking far ahead for a relatively long time (more than five seconds).
6. Grabbing legs.
7. Convulsions.

Experimental Procedure 2

Considering the rich behavior of a monkey freely moving in its cage and the great disparity of control observations [Insel (9)] this study was carried out in several stages. In the first stage, behaviors of a rhesus monkey freely moving in its cage were observed after administration of a medium dose of beta CCE (2 mg/kg).

The significance of these behaviors was evaluated as a function of their cumulated duration, and a behavioral scale was defined. In the second stage, the frequency of appearance of these behaviors in various individuals and their individual reproducibility were studied in order to select a limited number of symptoms reproducible in the same subject and in several animals during administration of beta CCE. In the third stage, the effects of increasing doses of beta CCE on the selected symptoms were studied in order to evidence a potential dose effect and the action kinetics of the molecule.

Animals were individually observed in their usual maintenance cages. Treatment was administered by use of a restraint box permitting the IV injection of the studied molecule. After administration the subject was then put back into its experimentation and behavioral observation cage for one hour.

A dose of 2 mg/kg beta CCE was administered in the first and second experimental phases. Three increasing doses of BCCE (0.5, 1 and 2 mg/kg) were administered to each one of eight rhesus monkeys in the third phase of the experiment.

Statistical Method

Means, standard deviations, and Mann and Whitney's nonparametric tests from obtained data are shown in Tables 2 and 3.

RESULTS

Experiment 1

All individual results are reported in Table 1. Behaviors are expressed in percent of observation time for each subject and for each dose (except for convulsions which are counted by number of crises).

The same results are expressed as means in Fig. 1. In placebo control situation, the four studied animals exhibit fairly similar behaviors (Table 1). Since animals were well accustomed to the experimental conditions, the predominant behavioral criteria are sleep and calm. Agitation, aggressiveness and convulsions were never observed.

At doses of 1 and 2 mg/kg BCCE induced a significant increase in staring ($p<0.05$) and agitation ($p<0.05$) behaviors in restrained rhesus monkeys. These observations are in agreement with results obtained by Crawley (5), Insel (9) and Ninan (16) using similar doses. A convulsive crisis was observed in the youngest animal after administration of 1 and 2 mg/kg BCCE.

Except for convulsive crises, this symptomatology was observed for all subjects within the first five minutes following administration of the molecule. The BCCE time effect varied as a function of the administered dose (30 minutes for 0.5 and 1 mg/kg and one hour for 2 mg/kg). Convulsive crises appeared 24 and 32 minutes after administration of 1 and 2 mg/kg respectively and lasted for 40 and 50 seconds.

Experiment 2

First phase: Observation of symptoms induced by the IV administration of 2 mg/kg beta CCE in rhesus monkeys ($n=8$). Twelve symptoms were observed during the treatment and not during the placebo session. Their intensity was evaluated as a function of the cumulated time of real symptom exhibition and mean intensity was calculated over eight subjects (Fig. 2).

The following behaviors were observed:

1. head motions
2. yawning
3. chewing: stereotype lip and jaw motions unrelated to food consumption
4. vocal sounds: all low or high pitch sounds
5. "Cooo" or "Kooo": unusual sound close to frog's croak, expressing a call (6,19)
6. lid closing (five seconds or more)
7. staring: the subject stared at an imaginary point or seemed absent
8. immobility: often related to staring. The animal keeps its body motionless
9. agitation: the monkey moves back and forth in its cage and moves in an unusual pattern
10. prostation: the animal curls up on itself, its head on its chest
11. convulsions
12. clutching: the animal holds its feet, hands or all limbs, or abnormally clutches cage bars

TABLE 1

BEHAVIORS INDUCED BY THE ADMINISTRATION OF THREE DOSES OF BCCE IN RESTRAINED RHESUS MONKEYS

Subjects	Doses mg/kg	Calm %	Behavioral Sleep %	Agitation %	Aggressiveness %	Staring %	Limb Holding %	Convulsions (nb. crises)
R1	Placebo	81.5	18.4	0.1	0	6.9	9.5	0
	0.5	80.3	19.7	0	0	2.2	0	0
	1	79.9	17.7	1.6	0.4	13.4	0.4	1
	2	93.5	4.9	0.6	0	20.8	38.2	1
R3	Placebo	57.1	40.5	0	0	5.5	0	0
	0.5	73.1	26.7	0	0	13.3	51.2	0
	1	80.2	15.4	0.2	0	22	35	0
	2	90.4	8.7	0.3	0.3	51.3	28.6	0
S4	Placebo	85.1	14.8	0	0	2	27.2	0
	0.5	80.8	39.2	0	0	7.2	10.1	0
	1	98.2	1	0.6	0.6	10	20.7	0
	2	81.2	18.3	0.5	0	21.3	0	0
T7	Placebo	63.8	36.5	0	0	4.3	0.9	0
	0.5	94.7	4.9	0.4	0	3.5	6.1	0
	1	87.2	8.1	0.9	0	15.1	4.3	0
	2	91	6.9	2.1	0	43.7	6.2	0

Behavioral criteria expressed in percent values.

Analysis of results in Fig. 2 shows the prevalence of three major behaviors as a function of their cumulated duration: staring, immobility and clutching. A second group of behaviors includes chewing, vocal sounds, lid closing and prostration. Other behaviors which appeared for a short time were: agitation, head motions, yawning, croaking and convulsions. After this first phase where behaviors were evidenced, fewer behaviors have to be selected which are the most reproducible and therefore the most significant after administration of BCCE.

Second phase: Selection of pathopmomonic behavioral criteria of the administration of beta carbolines. In order to select behavioral criteria, reproducibility of the symptoms observed in the same animal were observed after the administration of an identical dose (2 mg/kg) of BCCE. Symptom reproducibility was then verified among the eight experimental subjects.

Reproducibility was tested with an interval of two weeks for each animal. An example of results is shown in Fig. 3.

Results evidence five symptoms whose cumulated duration and

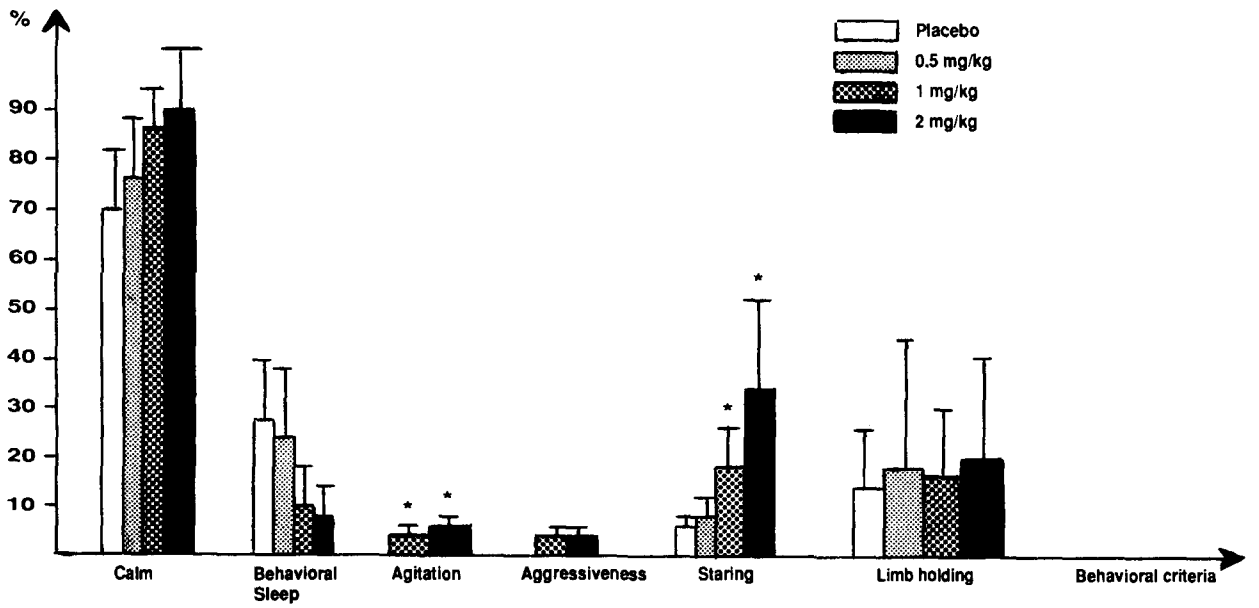

FIG. 1. Behaviors induced by the administration of three doses of beta CCE. Percent diagram of behavioral criteria. *Significance $p<0.05$, n = 4.

TABLE 2

BEHAVIORAL EFFECTS INDUCED BY BCCE IN RESTRAINED RHESUS MONKEYS

	Calm	Behavioral Sleep	Agitation	Aggressiveness	Staring	Limb Holding
Placebo	U1 = 9; U2 = 7	U1 = 7; U2 = 9	U1 = 8; U2 = 8	U1 = 8; U2 = 8	U1 = 10; U2 = 6	U1 = 9; U2 = 7
0.5 mg/kg	no signif.	no signif.	no signif.	no signif.	no signif.	no signif.
Placebo	U1 = 12; U2 = 4	U1 = 2; U2 = 14	U1 = 18; U2 = 0	U1 = 12; U2 = 4	U1 = 16; U2 = 0	U1 = 10; U2 = 6
2 mg/kg	no signif.	no signif.	signif. 5%	no signif.	signif. 5%	no signif.
Placebo	U1 = 14; U2 = 2	U1 = 1; U2 = 15	U1 = 16; U2 = 0	U1 = 10; U2 = 6	U1 = 16; U2 = 0	U1 = 10; U2 = 6
2 mg/kg	no signif.	no signif.	signif. 5%	no signif.	Signif. 5%	no signif.
Placebo	U1 = 35; U2 = 13	U1 = 10; U2 = 38	U1 = 40; U2 = 8	U1 = 30; U2 = 18	U1 = 42; U2 = 6	U1 = 30; U2 = 18
total	no signif.	no signif.	no signif.	no signif.	signif. 5%	no signif.

Statistical results Mann and Whitney's Nonparametric test.

reproducibility in the studied population are the greatest: chewing, lid closing, staring, immobility and clutching were selected because of their representativity for future investigations of the effects of increasing doses of BCCE. However, some behaviors such as convulsive crises, infrequent and of limited duration, or croaking cannot be totally disregarded and will be taken into consideration in the Discussion section.

Third phase: Effects of increasing doses of BCCE. The five selected symptoms were used to study the effects of increasing doses of BCCE (0.5, 1 and 2 mg/kg) in eight rhesus monkeys freely moving in their cages. Results are shown in Fig. 4. Schematically, the duration of all symptoms associated with the administration of increasing doses of BCCE seems to increase. This dose-effect is especially obvious for two behaviors. Staring and immobility and, to a lesser extent, for clutching. Statistical calculations evidence a significant difference between treatments with 2 mg/kg and placebo treatment for immobility ($p<0.05$) and fixed gaze ($p<0.01$). Although there is no significant difference between clutching at the highest BCCE dose and at the placebo dose, the mean duration of this behavior was longer after administration of 2 mg/kg BCCE than after administration of lower doses (0.5 mg/kg).

Regarding the kinetics of appearance of the various symptoms induced by the administration of 2 mg/kg BCCE, the following parameters were studied: latency, maximum activity (duration), intensity (subjective scale different for each behavior), attrition time, total time of observed behavior. Results are shown in Fig. 5.

It seems that chewing is the first behavior which appears

TABLE 3

BEHAVIORAL EFFECTS INDUCED BY BCCE IN RHESUS MONKEYS FREE TO MOVE IN THEIR CAGES

		Doses mg/kg			
Symptoms		Placebo n = 3	0.5 n = 5	1 n = 2	2 n = 8
Eyelid	mean	0	2.40	0.50	3.98
Closure	SEM	± 0	± 2.15	± 0.50	± 2.01
	U	—	NS	NS	*
Immobility	mean	0	5.2	7.5	10.125
	SEM	± 0	± 2.33	± 3.5	± 3.27
	U	—	*	NS	*
Staring	mean	0	4.6	7	11.93
	SEM	± 0	± 2.06	± 1	± 2.08
	U	—	*	NS	†
Chewing	mean	0	3.40	1	5.25
	SEM	± 0	± 2.22	± 1	± 1.54
	U	—	NS	NS	*
Clutching	mean	1.33	5.4	4.50	7.75
	SEM	± 1.33	± 2.92	± 0.5	± 4.15
	U	—	NS	NS	NS

*$p<0.05$, †$p<0.01$.

Statistical results: Mann and Whitney's U-test was used to compare results obtained after placebo administration of each dose of BCCE with results obtained after placebo administration.

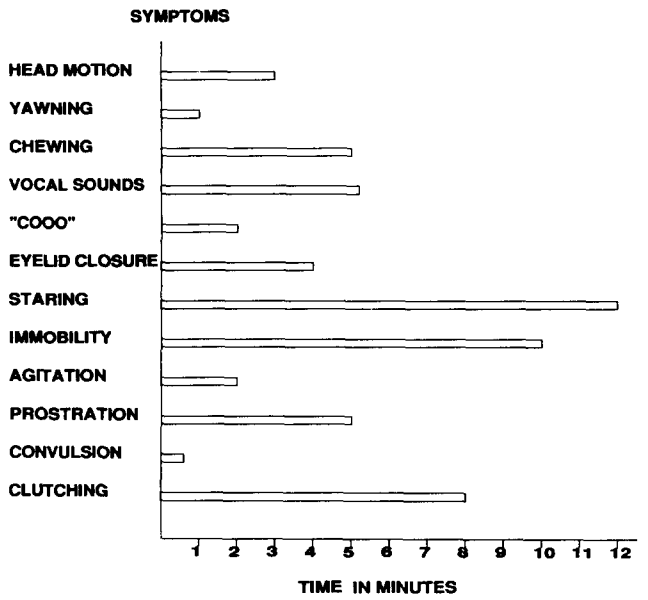

FIG. 2. Experiment 2: Phase 1. Symptoms induced by the administration of 2 mg/kg BCCE. (Cumulated time in minutes; n = 8.)

(within five minutes). After ten minutes other behaviors start appearing. Staring is the behavior which lasts the longest and is the last one to disappear. Other behaviors appear and disappear practically at the same time, i.e., between the 10th and the 40th minute posttreatment.

Comparison

The comparative study of results obtained on chair restrained and caged animals shows that the administration of BCCE triggers or enhances a number of behaviors regardless of the experimental situation. The greatest behavioral change is the amount of time dedicated for staring, a behavior which is relatively rare in a control situation, and which becomes prevalent after administration of BCCE and responds to a dose effect. Other behaviors are also modified after treatment, but more or less depending on the experimental conditions. For example, agitation significantly increases in restrained animals, but only slightly increases in unrestrained animals. This difference can be explained by the fact that the chair is the obstacle that the animal has to remove in order to express the excitation it feels. Agitation is then the only means of expression for the restrained animal, whereas an unrestrained animal can express its excitation by a greater array of behaviors (motion, clutching, etc.). Results obtained for limb holding or clutching can be given the same explanation. In fact, it is the same behavior expressed differently depending on experimental conditions. In its chair, the monkey grabs its legs and its chair; if it is free in its cage it grabs the bars. Regarding the clutching behavior a change was observed in the animals' preferential position in the cage: animals which used to stand in their cages crouched and remained in this position, clenching the floor bars.

Aggressiveness observed during the first, but not the second experiment can also be explained by the change in experimental conditions. During adaptation phases induced by treatment, restrained animals, placed side by side on the same support, are more enclined to display aggressiveness toward their congener than animals free to move in their cages.

DISCUSSION

For the nature of observed behaviors and for their kinetics, these results agree with those obtained by other teams which studied the behavioral effects of beta CCE in rhesus monkeys (4, 9, 16). In addition, it seems that restraint is not an obstacle to the observation of the main behavioral effects of beta carboline. Inversely, it facilitates the observation and the control of other parameters (ECG, EEG, etc.).

Results of the two experiments evidence convulsive crises

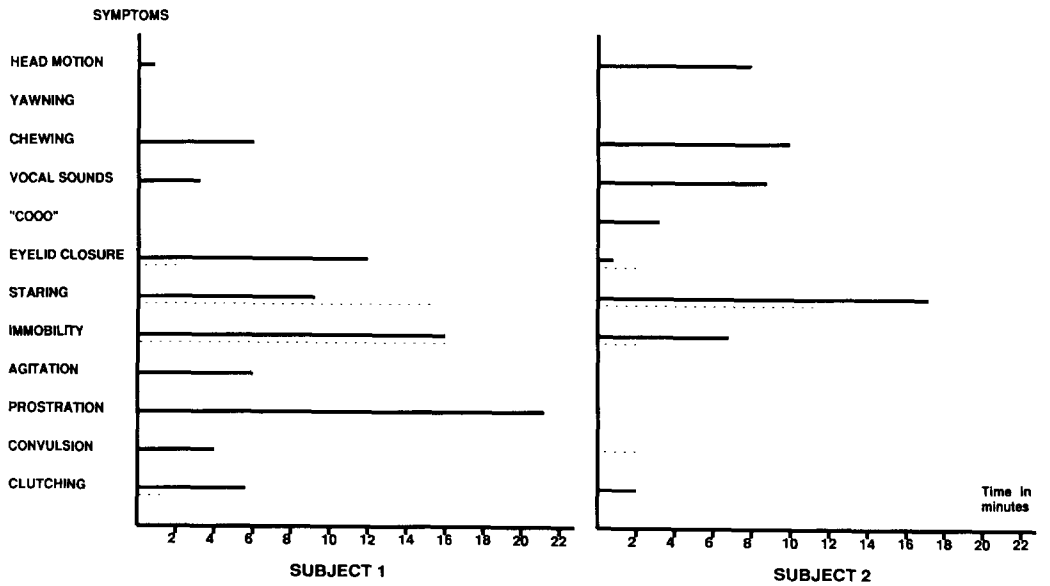

FIG. 3. Experiment 2: Phase 2. Reproducibility of behaviors induced by the administration of 2 mg/kg BCCE. Solid line: first observation; dotted line: Second observation.

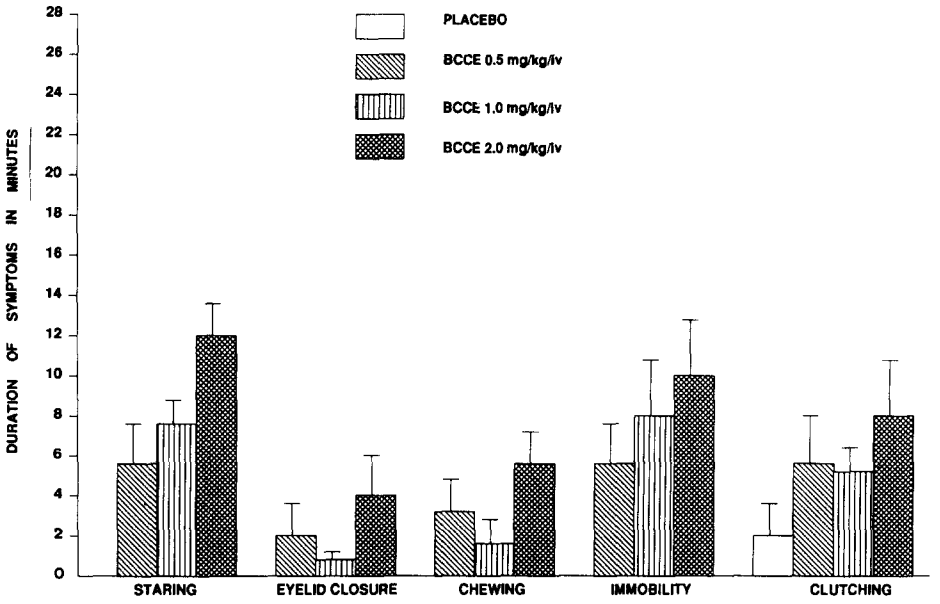

FIG. 4. Behavioral effects of increasing doses of BCCE in unrestrained rhesus monkeys.

obtained in the same proportions (one subject out of four in the first experiment and two subjects out of eight in the second experiment) and at the same doses (equal to or higher than 1 mg/kg IV). Beta CCE considered in monkeys as a proconvulsant compound appears to be convulsant in three subjects with no known pathological history. However, this observation does not contradict results obtained in mice where BCCE has a convulsant property (22). The convulsant effect observed in these animals could then be explained by a special sensitivity of the action mechanism of the compound capable of reducing the gabaergic activity and diminishing the chlor channel lumen (20). The increase in this gabaergic inhibition by beta carbolines in the benzodiazepine and GABA receptor complex could then stabilize and prolong discharges of slow waves (8).

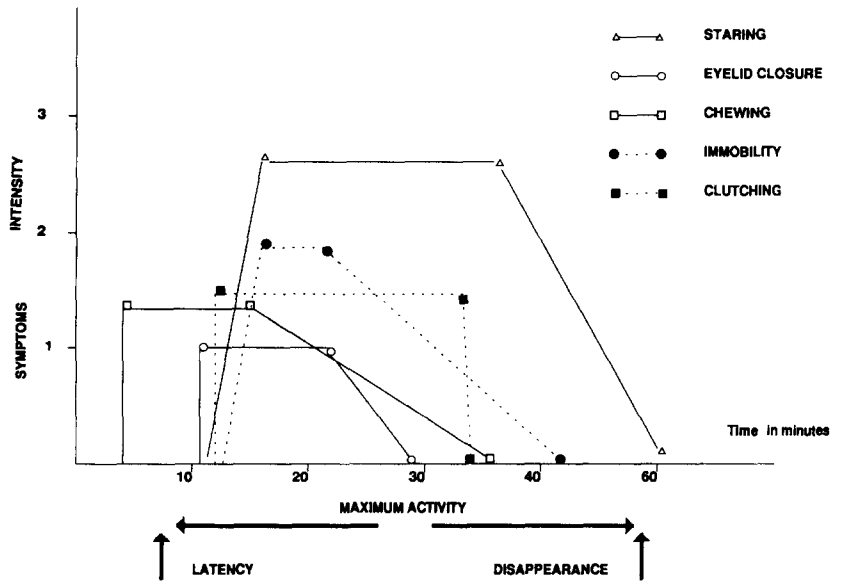

FIG. 5. Kinetics of the effects of 2 mg/kg BCCE [in order to clarify the figure, only points corresponding to the arithmetic mean (n = 8) are represented]. Symptoms intensity has been evaluated according to an arbitrary scale from 0 to 3: zero effect, light, moderate, strong. Definition of studied parameters: 1) Latency: time between the administration of the molecule and appearance of the studied behavior. 2) Maximum activity: time during which the observed behavior stays at maximum level. 3) Intensity: subjective scale used by the observer. Use of a different scale for each behavior. 4) Disappearance time: time between the administration of the molecule and the complete disappearance of the observed behavior. 5) Total time: time between appearance and disappearance of the observed behavior.

Aside from major behavioral changes observed after treatment with beta CCE, other symptoms of variable frequency and duration could be considered as the expression of an anxious state (4, 7, 21).

The systematic observation of certain behaviors such as staring, agitation, clutching or limb holding sometimes associated with aggressiveness reflect an unusual psychological state. Other behaviors, considered as minor because nonsystematically reproducible, such as lid closing or "COOO" or "KOOO" vocal sounds, also reflect a special situation. Lid closing in unrestrained animals after treatment, but not after placebo can be explained by a sedative effect leading to drowsiness and sleep. In reality, it seems more likely that this behavior is associated with immobility or staring, i.e., a wish to be isolated, to withdraw from the environment. The fact that in restraining chairs this behavior seems to be diminished by BCCE, confirms this interpretation. During restraint eye closing (assimilated in this case with behavioral sleep) is a usual behavior of rhesus monkeys, especially frequent when animals are in a soundproof chamber, with no environmental stimulus. Under this experimental condition the wish to withdraw and flee is, rather, expressed by staring. Cage floor clenching, sometimes associated with prostration, supports the idea that the monkeys' psychological state is not real fear or panic where they would try to escape by climbing the bars, but rather anguish with alternated phases of agitation and immobility.

During these phases of immobility the animal, frozen in a still position, closes its eyelids or stares. The "KOOO" criterion, not selected because of its variability among subjects is, however, a behavior to take into account because of its most unusual occurrence, reflecting, according to certain authors, an emotional disturbance (6,19).

CONCLUSION

The investigation of the effects of various doses of beta CCE in unrestrained and chair restrained rhesus monkeys evidenced three major facts: the first is the anxiogenic property of beta CCE. It seems that even moderate doses of beta CCE trigger a number of behaviors which can be interpreted as the reflection of an anxious state. The use of the rhesus monkey as anxiety model already suggested by Insel (9), Ninan (16) and Crawley (4) is supported by these results.

The second important fact brought to light by this investigation is the similarity in behavioral observations made under restraint and free conditions. This suggests that observation of chair restrained rhesus monkeys does not mask the main behavioral effects of beta CCE, and makes restrained animals suitable for the recording of various physiological parameters. The third fact is the appearance of convulsive crises after administration of BCCE at doses equal to or higher than 1 mg/kg IV. These convulsions triggered by doses very much lower than lethal doses suggest that certain animals have a specific sensitivity to BCCE or are generally sensitive to convulsant substances. However, these results have to be confirmed in other subjects by more extensive investigations.

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