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CCK8 Effects on Motivational and Emotional States of Rats Involve CCKA Receptors of the Postero-Median Part of the Nucleus Accumbens

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DAUGÉ, V , P STEIMES, M DERRIEN, N BEAU, B P ROQUES AND J FÉGER *CCK8 effects on motivational and emotional states of rats involve CCKA receptors of the postero-median part of the nucleus accumbens* PHARMACOL BIOCHEM BEHAV **34**(1) 157–163, 1989 —Administration of 3 fmol of cholecystokinin octapeptide (CCK8) into the postero-median nucleus accumbens (NAS) induced an hypoexploration measured using the four-hole box and an increase in the emotional states of rats observed in the elevated plus maze These effects seem likely to involve CCKA receptors since they were reversed by the selective CCKA antagonist L364,718 (100 μg/kg, 200 μg/kg IP) and not observed after injection of 0 1 to 1000 fmol unsulfated cholecystokinin octapeptide (CCK8NS) in the same region On the other hand, CCK8 or CCK8NS injected into the anterior NAS did not significantly modify these behaviors These results support the neuroanatomical heterogeneity in the distribution of CCK and its binding sites in the NAS, but raise the question of the presence of CCKA receptors not detected in binding studies and of the behavioral effects mediated by CCKB receptor stimulation in this structure

Cholecystokinin octapeptide Cholecystokinin octapeptide unsulfated CCKA receptors
Postero-median nucleus accumbens Anterior nucleus accumbens Exploration Emotionality Rats

THE nucleus accumbens (NAS) is a part of the striatum included in the so-called "ventral striatum" according to Heimer and Wilson (14). This subcortical structure is anatomically characterized by the importance of its relations with the limbic system (cingular cortex, lateral hypothalamus, hippocampus, amygdala . . .) (18,20) and with subcortical nuclei related to the initiation and control of motor behavior (globus pallidus, substantia nigra .) (20) The NAS contains high densities of sulfated cholecystokinin octapeptide CCK8 and CCK8 receptors (7, 12, 28). The finding that CCK8 coexists with dopamine (DA) in the mesolimbic system, including the projections to the NAS, has generated many studies on the functional interaction between these two neurotransmitters [reviewed in (4)] Several results indicate that CCK8 exerts DA antagonist-like effects (10, 27, 29, 32, 33), whereas others support a potentiation of DA agonist effects (3,6) These discrepancies might be due in part to the anatomical and biochemical heterogeneity of the NAS Indeed, this nucleus may be divided in two parts in relation to CCK8 terminal and receptor distribution. The postero-median NAS receives CCK8 terminals originating from the ventral tegmental area, most of them also containing DA (15,16). On the other hand, the anterior NAS receives CCK8 terminals arising from both the ventral tegmental area and from the cortical structures (9), and has been shown to contain high levels of CCK central binding sites (B-type CCKB) as compared to the posterior NAS (22) Conversely, no CCK peripheral binding sites (A-type CCKA) have been detected in the rat NAS. In relation to the heterogeneity of NAS, differential effects of CCK8 have been observed in biochemical studies Thus, CCK8 (0.1 nM) was able to increase the K^+-evoked DA release or the basal DA release (CCK8, 0.1, 1 μM) in the posterior region, while CCK8 (1–100 nM) induced a decrease only on the K^+-evoked DA release in the anterior region (30) Furthermore, opposite effects of CCK8 have been found on the DA-sensitive adenylate cyclase from the anterior and the posterior regions (25) On the other hand, CCK8

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has been reported to both antagonize the amphetamine-evoked release of presynaptic DA and to potentiate the ability of DA to inhibit postsynaptic neurons in the postero-medial part of the NAS (4, 24, 31) In most pharmacological studies, CCK8 locally injected into the NAS did not modify motor activity of rats However, some behavioral studies have emphasized the importance of placing the animals under stimuli such as a novel environment in order to observe the proper effects of CCK8 administered into the NAS (5, 17, 29) Thus, under these conditions, we have recently reported a decrease in exploratory behavior after injection of CCK8 into the NAS at very low doses [0 1 fmol to 100 pmol, (5)] Likewise, very weak concentrations of CCK have been shown to be efficient on active and passive avoidance behavior (10,29) These last studies are the only two which have reported an effect of the unsulfated CCK8 (CCK8NS) in the NAS

We have shown in previous studies that in the four-hole box, the hypoexploration induced by CCK8 injected into the NAS was not related to motor disturbances (5) The four-hole box allows the experimenter to measure oriented responses of exploratory behavior (26) Since this behavior represents a complex interplay of curiosity and emotionality, we decided to use also the elevated plus maze in order to investigate the role of emotional factors in CCK8-induced hypoexploration. This test, validated by Pellow *et al* (23) as a measure of anxiety in the rat, has advantages over other conflict tests, as it requires only spontaneous activity of the animals Therefore, in this study, we have investigated the effects of CCK8 and CCK8NS in order to distinguish their role on emotional behavior of rats by use of the elevated plus maze as well as the four-hole box test Furthermore, owing to the complexity of the CCKergic network in the NAS, the effects of CCK8 and CCK8NS were compared after local injection into the anterior or postero-median part of the NAS

GENERAL METHOD

Animals

The subjects were 145 male Wistar rats (centre d'élevage Depré) weighing 200–220 g at the time of surgery The animals were housed in groups of ten with food and water made available ad lib

Drugs

Cholecystokinin octapeptide sulfate (CCK8) and cholecystokinin octapeptide unsulfated (CCK8NS), synthesized in the laboratory of B P Roques, were dissolved in 0 9% saline The following quantities were injected in each postero-median NAS CCK8 0.1, 1, 3 fmol/0 2 μl, CCK8NS 0 1, 1, 10, 100, 1000 fmol/0 2 μl; in each anterior part of NAS CCK8 1, 10, 100, 1000, 10,000 fmol/0 2 μl, CCK8NS 10, 100, 1000, 10,000 fmol/0 2 μl L364,718 (a generous gift of Merck Laboratories) used as antagonist of CCKA receptors was suspended in carboxymethylcellulose (0 05%) The animals received 100 μg/kg or 200 μg/kg IP

Apparatus

Four-hole box This automated apparatus consisted of a black metallic square box (45 × 45 × 24 cm) illuminated (175 lux) from the top In each of the corners, there was a small corridor (length = 8 cm) at the end of which a hole was drilled (diameter = 3 5 cm) 4 cm above floor extended by a metallic tube [length = 8 cm, for details see (26)] A photoelectric detector was placed at the center of each hole The number and the duration of beam

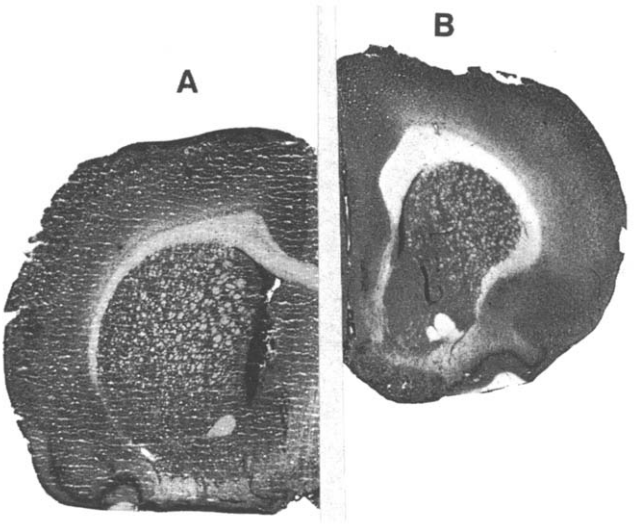

FIG 1 Microphotographs showing a typical cannula placement into the postero-median nucleus accumbens (A), or into the anterior nucleus accumbens (B)

"interruptions" served as measures of exploratory behavior and were registered on a chart recorder

The rat was placed in the middle of the arena and the following parameters were recorded (a) latency time of the first hole visit, (b) number and duration(s) of nose pokes monitored for 15 min, (c) hole switching analysis which indicates whether animals repeatedly visit the same hole or switch to another one (%), (d) hole sequences showing the percentage of adjacent hole visits and skipped hole visits

Elevated plus maze The elevated plus maze was a wooden apparatus It consisted of two open arms, 50 × 10 cm, and two enclosed arms, 50 × 10 × 40 cm, with an open roof arranged such that the two open arms were opposite to each other The maze was elevated to a height of 50 cm and illuminated from the top The measurements were taken by an observer sitting in the same room as the maze (23) At the beginning of the test, the rat was placed in the center of the maze facing an open arm Entry into an arm was defined as the animal placing all four paws into the arm The cumulative time spent in, as well as the number of entries made into open or closed arms were recorded during a five-minute test session The results are expressed as the total number or time spent in open and closed arm visits and as a percent of the total number or time spent in open arms over total number or time spent in open and closed arms visits The use of this test for detecting anxiolytic and anxiogenic drug effects was validated behaviourally, physiologically and pharmacologically by Pellow *et al* (23)

Histology

After completion of the experiment, overdoses of sodium pentobarbital were administered to the animals The brains were removed, frozen and cut on a microtome The slices (50 μm) were stained with cresyl violet Figure 1 represents a trace of injection needle into the two regions of the NAS (A = postero-median, B = anterior)

Data Analysis

The results of the four-hole box and the elevated plus maze tests were each analysed by a one-factor (treatment) analysis of

variance (ANOVA). The significant differences between individual means were then identified using a Dunnett post hoc test (comparison vs saline group), or a Newman-Keuls test (pairwise comparison).

EXPERIMENT 1

Surgery

Ninety rats were anesthetized by an IP injection of ketamine (100 mg/kg) and bilaterally implanted with stainless-steel cannula guides (25 gauge) 1 5 mm above the postero-median NAS The stereotaxic coordinates according to Paxinos and Watson (21) were 1 2 mm anterior to bregma, lateral ±1.2, ventral 7 mm below the skull The cannula guides were kept clear with wire stylets The animals were tested 8–10 days after surgery

Intracerebral Injection

The animals were injected into the postero-median NAS via bilateral 30 5-gauge stainless-steel needles attached to a 2 µl microsyringe (Hamilton) by polyethylene tubing Drugs or saline were administered by an infusion pump (Precinorm) in a constant volume of 0 2 µl for 120 sec. The needles were left in situ for 30 sec to allow for diffusion away from the cannula guide.

Fifteen rats were used for the experiment with CCK8 Three doses were chosen on the basis of previous studies (5) CCK8 0 1 fmol (n=8), 1 fmol (n=8), 3 fmol (n=8) Thirty rats were used for the experiment with CCK8NS Five doses were studied CCK8NS 0 1 fmol (n=8), 1 fmol (n=8), 10 fmol (n=8), 100 fmol (n=8), 1000 fmol (n=8) The control group received 0.2 µl of saline (n=8) In the experiment with L364,718, four groups were used for each dose of L364,718 control (n=8), CCK8 3 fmol (n=8), L364,718 100 µg/kg (n=8), L364,718 100 µg/kg + CCK8 3 fmol (n=8); control (n=8), CCK8 3 fmol (n=8), L364,718 200 µg/kg (n=8), L364,718 200 µg/kg + CCK8 3 fmol (n=6).

Each animal was injected twice separated by a minimum 48-hr interval The animals were tested in the four-hole box (for 15 min), 15 min after injection into the NAS Immediately after, the animals were placed in the elevated plus maze for 5 min L364,718 was injected IP 60 min before intraaccumbens administration of CCK8 or saline.

RESULTS

Four-Hole Box

CCK8 injected into the postero-median NAS produced a marked decrease in exploratory behavior. One-way analysis of variance confirmed that there were statistically reliable effects between groups (control, CCK8 0.1, 1, 3 fmol) for the number of hole visits. $F(3,28)=11\ 2$, $p<0.01$, and for the time spent in hole visits $F(3,28)=6.9$, $p<0.05$. Post hoc Dunnett's test confirmed that the "group" effects were attributable to CCK8 0 1, 1, and 3 fmol which were significantly different from the control group ($p<0.001$) for both the number and the time spent on hole visits (Fig. 2A) The latency time was not changed and the results of analysis of hole sequences showed that injection of CCK8 did not modify the adjacent holes and skipped hole visits (not shown)

On the other hand, CCK8NS injected into the postero-median NAS did not modify the exploratory behavior of rats (Fig. 2B) One-way analysis of variance revealed no statistically different effects between groups (control, CCK8NS 0.1, 1, 10, 100, 1000 fmol) for the number of hole visits· $F(5,42)=1.27$, and for the time spent in hole visits, $F(5,42)=1\ 4$ The latency time was not changed and the results of the analysis of hole sequences showed that injection of CCK8NS did not modify the adjacent holes and skipped hole visits (not shown).

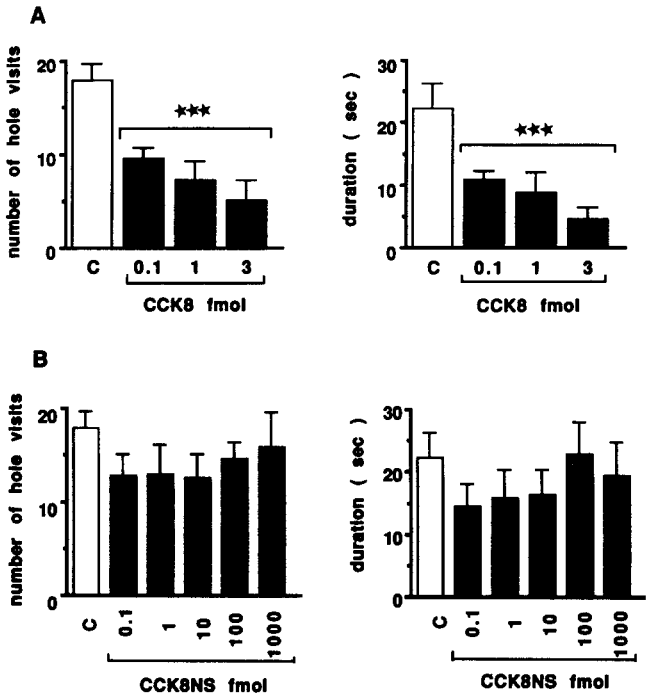

FIG 2 Exploratory behavior of rats over 15 min in the four-hole box test (A) Fifteen min after injection of CCK8 into the postero-median NAS (B) Fifteen min after injection of CCK8NS into the postero-median NAS The results are expressed in means ± S E M of the number and the duration of hole visits C=control group n=8 for each group ***$p<0$ 001 Dunnett's test

L364,718 (100 or 200 µg/kg IP), a highly selective antagonist of CCKA binding sites injected 60 min before CCK8 administration into the NAS, did not modify the rats' behavior, but antagonized the hypoexploration. One-way analysis of variance confirmed that there were statistically reliable effects between groups (control, CCK8 3 fmol, L364,718 100 µg/kg, L364,718 100 µg/kg + CCK8 3 fmol) for the number of hole visits $F(3,28)=12\ 72$, $p<0.01$, and for the duration of hole visits $F(3,28)=8\ 81$, $p<0\ 01$ Post hoc Newman-Keuls confirmed that 3 fmol of CCK8 was significantly different from the control group for the number and the duration of hole visits ($p<0.01$). Furthermore, the CCK8 3 fmol + L364,718 100 µg/kg group was significantly different from the CCK8 group ($p<0.01$) (Fig. 3A). For the experiment with 200 µg/kg of L364,718, the CCK8 3 fmol + L364,718 group was significant as compared to the CCK8 3 fmol group for the number and for the duration of hole visits ($p<0.01$) Fig. 3A.

Elevated Plus Maze

CCK8 (0 1, 1, 3 fmol) injected into the postero-median NAS reduced the total number of arm entries that was significant on the ANOVA, $F(3,28)=3\ 23$, $p<0.05$. Table 1 shows that CCK8 (3 fmol) induced a significant effect as compared to the control group ($p<0.05$). The time spent in the open and closed arms was not significantly different from the controls $F(3,28)=1.02$. Treatment with CCK8 significantly decreased the percentage of open

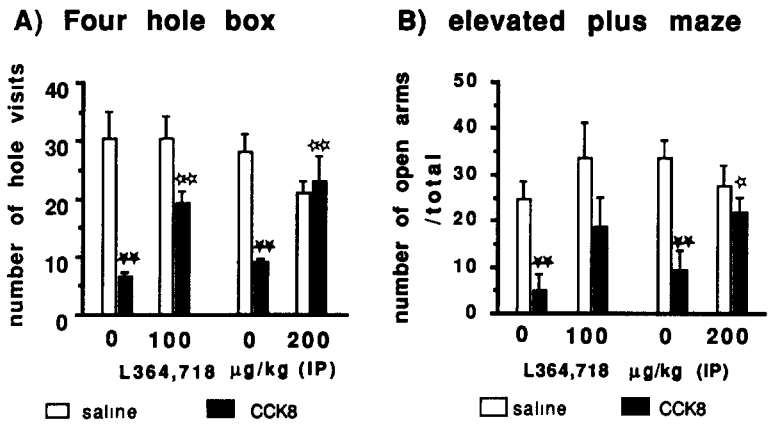

FIG 3 Antagonism of CCK8 (3 fmol) effects when injected into the postero-median NAS by L364,718 (100 or 200 µg/kg) (A) Mean ± S E M of the number of hole visits in the four-hole box 15 min after injection of CCK8 (B) Mean ± S E M ratio of the number of open-arm visits over the number of total-arm visits (elevated plus maze) Rats were tested for 5 min just after the four-hole box exposure L364,718 was injected IP 60 min before CCK8 intraaccumbens n = 8 for each group, n = 6 for L364,718 (200 µg/kg) + CCK8 3 fmol ★★$p<0$ 01 vs control groups ☆$p<0$ 05, ☆☆$p<0$ 01 vs CCK8-treated group

arm entries, $F(3,28) = 3.13$, $p<0.05$, and the percentage of the time spent in the open arms, $F(3,28) = 4$ 10, $p<0$ 01 Post hoc Dunnett's test confirmed that the "group effects" were attributable to CCK8 3 fmol ($p<0$ 05) for the percentage of open-arm entries and to CCK8 1 and 3 fmol ($p<0$ 05) for the percentage of the time spent in the open arms (Fig 4)

In the experiment with L364,718, 100 µg/kg partially reversed the percentage of open-arm entries and the percentage of the time spent in the open arms, whereas 200 µg/kg completely antagonized the CCK8 effects ($p<0.01$) (Fig 3B)

CCK8NS (0 1, 1, 10, 100, 1000 fmol) injected into the postero-median NAS did not modify the rats' behavior in the elevated plus maze (Table 1, Fig 4) The one-way analysis of variance indicated no significant different effect between groups for the total number of arms entries, $F(5,42) = 1$ 5, for the time spent in the open and closed arms, $F(5,42) = 1$ 25, and for the percentage of open-arm entries, $F(5,42) = 0$ 7, and the percentage of the time spent in the open arms, $F(5,42) = 1$ 66

TABLE 1

MEAN ± S E M OF THE TOTAL ENTRIES AND DURATION OF ARMS VISITS FOR 5 MIN IN THE ELEVATED PLUS MAZE AFTER INJECTION INTO THE POSTERO-MEDIAN NAS OF CCK8 OR CCK8NS

Drugs		Total Entries	Total Duration
Control		8 7 ± 1 5	205 4 ± 10 4
CCK8	0 1 fmol	8 6 ± 1 3	225 2 ± 18 9
	1	7 9 ± 1 1	235 2 ± 9 4
	3	4 1 ± 0 8*	197 0 ± 25 6
CCK8NS	0 1 fmol	7 0 ± 1 5	227 5 ± 13 3
	1	9 9 ± 1 2	216 6 ± 12 6
	10	8 0 ± 2 7	184 1 ± 21 0
	100	5 3 ± 0 7	243 5 ± 10 0
	1000	6 6 ± 1 2	219 0 ± 16 9

*$p<0$ 05 Dunnett's test
n = 8 for each group

EXPERIMENT 2

Surgery

Fifty-five rats were stereotaxically implanted with stainless-steel cannula guides following the same procedure described in Experiment 1 The coordinates, according to Paxinos and Watson (21), were 2 5 mm anterior to bregma, lateral ± 1 5 mm, ventral 7 mm below the skull

Intracerebral Injection

The injections were performed using the same procedures and schedule described in Experiment 1

Twenty-two rats were used for experiment with CCK8 Five doses were studied. CCK8 1 fmol (n = 8), 10 fmol (n = 8), 100 fmol (n = 8), 1000 fmol (n = 8), 10,000 fmol (n = 8) Twenty rats were used for the experiment with CCK8NS Four doses were studied CCK8NS 10 fmol (n = 8), 100 fmol (n = 8), 1000 fmol (n = 8), 10,000 fmol (n = 8) Control group received 0 2 µl of saline (n = 8)

RESULTS

Four-Hole Box

CCK8 or CCK8NS injected into the anterior NAS induced a slight, but not significant increase of the number and duration of hole visits (Fig 5) One-way of analysis of variance revealed no statistically different effects between groups (control, CCK8 1, 10, 100, 1000, 10,000 fmol) for the number of hole visits $F(5,42) = 1$ 27, and the duration of hole visits $F(5,42) = 1.04$. Similarly, one-way analysis of variance revealed no statistically different effects between groups (control, CCK8NS 10, 100, 1000, 10,000 fmol) for the number of hole visits $F(4,35) = 1$ 50, and the duration of hole visits· $F(4,35) = 0$ 97 The latency time was not changed and the results of the analysis of hole sequences showed that injection of CCK8 or CCK8NS did not modify the adjacent holes and skipped hole visits (not shown)

Elevated Plus Maze

Neither CCK8 nor CCK8NS modified the rats' behavior in the

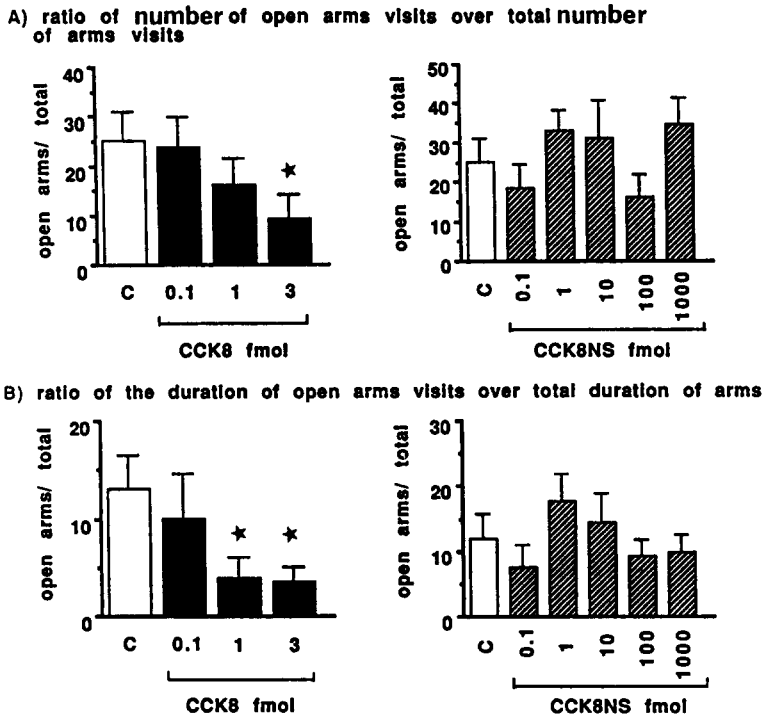

FIG 4 Mean ± S E M ratio of the number of open-arm visits over the number of total-arm visits, ratio of the time spent in open-arm visits over total time spent in open-arm visits Rats were injected with CCK8 or CCK8NS into the postero-median NAS and tested for 5 min in the elevated plus maze just after the four-hole box exposure n = 8 for each group $\star p<0$ 05 Dunnett's test

elevated-plus maze (not shown) One-way analysis of variance revealed no statistically different effects between groups (control, CCK8 1, 10, 100, 1000, 10,000 fmol) for the total number of arm entries, $F(5,42)=0.5$, for the time spent in the open and closed arms, $F(5,42)=1.30$, for the percentage of open-arm entries, $F(5,42)=0.92$, and for the percentage of the time spent in the open arms, $F(5,42)=1.64$ One-way analysis of variance indicated no statistically different effects between groups (control, CCK8NS 10, 100, 1000, 10,000 fmol) for the total number of arms entries, $F(4,35)=0.54$, for the time spent in the open and closed arms, $F(4,35)=0.10$, for the percentage of open arms entries, $F(4,35)=1.29$, and for the percentage of the time spent in the open arms, $F(4,35)=1.01$

GENERAL DISCUSSION

In order to study the effects of CCK8 in relation to the heterogeneous distribution of CCK terminals and receptors in the rat NAS, the previously used experimental procedure (5) was modified by reduction of injected volume of drugs (0 2 µl in place of 1 µl) and the behavior was observed 15 min after injection Using these new conditions, the injection of CCK8 into the postero-median NAS produced the same reduction in exploratory behavior measured in the four-hole box as those previously described (5) On the other hand, CCK8NS (0.1–1000 fmol) did not modify the exploratory behavior of the animals after injection into the same region of NAS

In the elevated plus maze, CCK8 (3 fmol) injected into the postero-median NAS induced a decrease of the total number of entries confirming the effect of CCK8 in decreasing the explor-

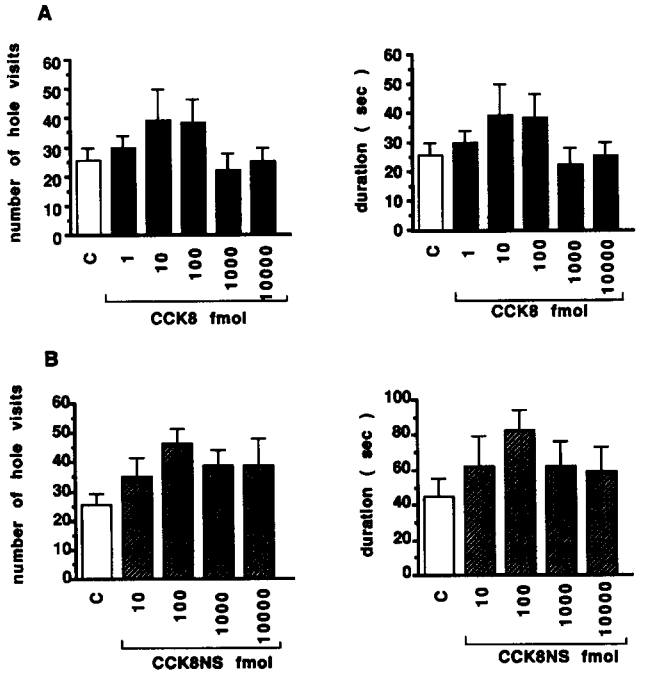

FIG 5 Exploratory behavior of rats over 15 min in the four-hole box test (A) Fifteen min after injection of CCK8 into the anterior NAS (B) Fifteen min after injection of CCK8NS into the anterior NAS The results are expressed in means ± S E M of the number and the duration of hole visits C = control group n = 8 for each group

atory activity of animals The ratio open/total arms visits was significantly decreased at 3 fmol for the number and at 1 and 3 fmol for the time spent in open arms, indicating an anxiogenic-like effect for this peptide This is supported by the lack of significant correlation between the percentage of entries into open arms over total arms visits and the total number of entries for the 3 doses of CCK8 ($r = 8$, $\gamma = 1$) Indeed, other sedation-causing drugs, such as haloperidol, seem to decrease the total number of arms visits without altering the ratio open/total arm visits [Pellow *et al* (23)]

In contrast to CCK8, the unsulfated analog CCK8NS (0 1–1000 fmol) injected into the postero-median NAS did not change the rats' behavior in the elevated-plus maze

Therefore, our results suggest that the site through which CCK8 induces an hypoexploration and an increase of rat emotionality is not the central-type CCKB receptor, but the peripheral CCKA type This is supported by suppression of the CCK8-induced effects by L364,718, a highly potent and selective antagonist of CCKA binding sites (1) The pharmacology of this receptor type appears to match that of the receptor inducing the CCK8-potentiating effect of DA responses in the postero-median NAS described by Crawley *et al* (3) This is a rather striking result since, at this time, binding and autoradiographic studies indicate the presence of only one class of binding sites in the rat NAS corresponding to B or central CCK8 receptors in NAS for which the affinity of CCK8NS was only about five to ten times lower than CCK8 (8, 12, 19, 22) However, measurable levels of the peripheral-type CCK receptor have been described in rat brain structures such as the solitarius tractus nucleus, the area postrema, the interpeduncular nucleus and the posterior hypothalamic nucleus (19)

The other goal of this study was to examine the effects of CCK8 and CCK8NS after injection into the anterior region of the NAS Both compounds produced no significant modifications of the rats' behavior in the four-hole box and the elevated plus maze tests, although a slight increase in exploration in the four-hole box was obtained after injection of 10 and 100 fmol of CCK8 or CCK8NS (Fig 5) The anterior part of the NAS is rich in CCKB receptors but their involvement in the behavior of rat is not clearly understood Only two studies have reported an effect of CCK8NS administered into the NAS Thus, CCK8 or CCK8NS were shown to antagonize the hypolocomotion induced by low doses of apomorphine [10 ng into NAS, (29)] Furthermore, Fekete *et al* (10) described a facilitation of the extinction of active avoidance behavior and an attenuation of the retention of passive avoidance behavior after injection of CCK8 or CCK8NS in the fmol dose range However, the implication of one or both types of CCK receptors in these responses has not been studied

In conclusion, the modulatory effects of CCK8 in the NAS seem to be dependent on the motivational and emotional state of rats These effects are restricted to the postero-median part of the NAS and appear to involve CCKA binding sites The lack of CCK8 actions at the level of the anterior NAS emphasized the heterogeneity of this structure and raises the question of the role played by CCKB receptors in this part of the NAS The recently described immunohistochemical and connectional singularities of various compartments in the rat ventral striatum, supporting the differences between the rostral and the caudal part of this structure (13), can help to better understand the role of CCK in the rat NAS The recent development of a selective agonist (2) and antagonist (11) for CCKB binding sites should clarify the physiological implications of this receptor type in the central nervous system

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