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Cholecystokinin Receptors and Memory: A Radial Maze Study

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HARRO, J. AND L. ORELAND. *Cholecystokinin receptors and memory: A radial maze study.* PHARMACOL BIOCHEM BEHAV 44(3), 509–517, 1993.—CCK receptor agonists and antagonists have repeatedly been demonstrated to improve and impair, respectively, learning and memory functions. However, all studies to date have exploited avoidance paradigms. In the present study, the effect of some CCK receptor agonists and antagonists on the ability to learn an appetitively motivated task and to influence spatial working memory was investigated. In the first experiment, drugs were given immediately after each training session in the radial maze and the animals were tested, drug-free, during a 2-week period. After the initial treatments with caerulein, an unselective CCK receptor agonist (100 ng/kg SC), the animals were slightly less successful to obtain food pellets during the sessions on the first 2 days; whereas proglumide, an unselective CCK receptor antagonist (1 mg/kg SC) was without any effect. However, on the following days, all the three groups of rats (saline, caerulein, and proglumide) performed in a similar way. In the second experiment, drugs were given before each test session to well-trained animals. Scopolamine (0.15 and 0.3 mg/kg IP), the reference amnestic drug, produced dose-dependent impairment of working memory in the radial maze test. Proglumide (1 and 10 mg/kg SC) and devazepide, (a selective CCK-A receptor antagonist; 0.01 and 1 mg/kg SC), as well as caerulein (0.01, 0.1 and 1 μg/kg SC) and CCK-4 (a selective CCK-B receptor agonist; 25 and 50 μg/kg SC) had no reliable effect. When caerulein (0.1, 2 and 10 μg/kg SC) was given together with scopolamine (0.15 mg/kg IP), the lower doses were without effect, whereas the highest dose of the peptide tended to potentiate the action of scopolamine, probably due to its sedative action. On the other hand, the selective CCK-B receptor agonist CCK-4 (50 μg/kg SC), administered together with scopolamine (0.15 mg/kg IP), did not induce sedation, but caused a further increase in the number of erroneous arm entries and a changed pattern of arm exploration. Taken together, the results support the idea that the effects of CCK receptor ligands on learning and memory differ in aversively vs appetitively motivated paradigms and depend upon the receptor subtype activated or blocked.

CCK receptors Caerulein CCK-4 Proglumide Devazepide Radial maze Memory Anxiety Scopolamine

CHOLECYSTOKININ (CCK), a neuropeptide abundantly present in the cerebral cortex and limbic regions (9), has been implicated to play a significant role in feeding (33), sedation (45), pain perception (2), anxiety (37), and exploratory behaviour (21). CCK appears also to modulate memory processes, as recently reviewed by Itoh and Lal (24). CCK-related peptides, if injected either peripherally or intracerebrally, prevent experimental amnesia and delay extinction of the already-learned tasks. Furthermore, CCK receptor antagonists not only prevent the effects of CCK treatments but impair memory on their own, suggesting that endogenous CCK is involved.

However, the physiological meaning of CCK for the learning and memory processes is not at all clear. First, as vagotomy blocks the promnestic action of peripherally administered CCK (33) and centrally administered CCK is believed to reach peripheral blood circulation in reasonable quantities (10,36), it has not yet been possible to establish if CCK has any action on memory through the receptors in the brain. Second, the use of selective drugs for CCK receptor subtypes has yielded contradictory results. CCK receptors are currently divided into two major groups: CCK-A receptors localized in the gastrointestinal system as well as in certain regions of the central nervous system, and CCK-B receptors that are widespread in the brain (17,32). Therefore, possible peripheral effects of CCK receptor ligands on learning and memory would be expected to be attributable to CCK-A receptors. Indeed, selective CCK-A receptor antagonists such as devazepide and lorglumide can produce amnesia (39). However, short COOH-terminal fragments of the parent CCK molecule, known to interact with CCK-B receptors only, can also exert promnestic influences (17). To make the matter more confusing, CCK-B

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agonists have been reported to facilitate (17) and impair (29) the retention of passive avoidance response.

Two main approaches to study the effect of a drug on learning and memory are to use either appetitively or aversively motivated tasks (4). Surprisingly, we were not able to find any reference for a study on memory effects of CCK receptor ligands in appetitively motivated paradigms. Thus, almost all what is known about CCK and memory has been collected from experiments that have exploited either active or passive-avoidance behaviour (24). Very recently, Takashima and colleagues (40) have also reported about an antiamnestic action of caerulein, an unselective CCK receptor agonist, in an aversively motivated spatial memory task (Morris water pool test), suggesting that spatial memory can be modulated through CCK receptors. A simple explanation for the lack of studies using appetitively motivated tests can be derived from the characterization of CCK as one of the main satiety factors. However, a problem with the avoidance techniques is that they are sensitive to the drugs that influence anxiety (7,28,42). Recently, the anxiogenic-like action of CCK-peptides in rats and monkeys has been characterized after peripheral and intracerebral injections (for reviews see ref. 21,37,44). These findings are supported by clinical studies showing that CCK-4 is a potent panicogenic drug (5,6,12). CCK-8 has also been demonstrated to induce conditioned taste aversion (13), suggesting that the facilitatory effect of CCK receptor stimulation on avoidance learning may be, at least in part, related to its aversive nature. Thus, the impact of CCK in memory might come from the influence of emotions on learning abilities and memory functions.

To test if CCK receptor stimulation and blockade could affect appetitively motivated learning, we have taken advantage of the radial maze test, which was developed to measure spatial working memory in rats and uses food motivation as the stimulus (34; see ref. 31 for review). The results obtained suggest that certain manipulations on CCK-ergic neurotransmission may affect performance in this test, but the behavioural changes induced are not consistent with predictions from avoidance studies; and the receptor subtype involved is probably distinct.

METHOD

Subjects

The subjects for the experiments described were 24 male Sprague–Dawley rats, obtained from Alab (Sollentuna, Sweden) at the age of 2 months. They were housed 4 per cage in a room with stable temperature and reversed 12L : 12D h. All testing was carried on during the dark phase (1 a.m.–7 a.m.) in a dim light during a period from July to September, 1991. The animals were habituated to the housing conditions during 10 days after arrival. In this period, they were fed ad lib. Prior to the first testing, rats were fasting for 20 h and on the test days food was available only during 30 min after each session. On weekends, food was available during one or two 30-min periods per day. Such a feeding schedule maintained the animals at 85% of their initial bodyweight (250 g in average) plus 5 g weight gain per week in average.

Drugs

Scopolamine hydrobromide (Sigma Chemical Co., St. Louis, MO) was given IP, all other drugs subcutaneously. Devazepide (Merck Sharp & Dohme, West Point, PA) was suspended in saline with a help of few drops of Tween 85 (Sigma), yielding an approximately 1% solution of Tween, which was also used as a vehicle while appropriate. CCK-4 (Bachem, Torrance, CA) was dissolved in 100 μl 0.1 M HCl and thereafter diluted with saline. Caerulein (Bachem) and proglumide (Rotta Pharmaceutici, s.p.a. Milan, Italy), as well as scopolamine, were dissolved in saline. The injection volume was 2 ml/kg for devazepide and 1 ml/kg for all other drugs. In Experiment 1, caerulein and proglumide were injected immediately after each radial maze session. In Experiment 2, scopolamine and devazepide were given 20–40 min before testing whereas all other compounds were injected 10–20 min before the beginning of the behavioural test. The doses of CCK receptor agonists and antagonists were chosen on the basis of previous evidence from memory studies (summarized in ref. 24) and our experience from studies on exploratory behaviour (summarized in ref. 21).

Testing Conditions

Behavioural testing was conducted in an elevated eight-arm radial maze made of aluminium plate. The arms of the maze had low side walls to alleviate the aversiveness of open areas. Each arm (60 cm long and 12 cm wide) extended from an octagonally shaped central platform (32 cm in diameter). There were food cups at the end of each arm. Small pieces of laboratory rat chow were placed into the food cups, one piece per a cup, and the cups were not rebaited during the test. The observer was sitting in the same room, 2 m apart from the center of the maze, and recorded the measures taken (the sequence of successive arm entries and the total time until the animal consumed the last pellet) using a keyboard connected to a microcomputer. The maximal length of a session was 10 min. When placed on the central platform, rats were faced different arms on different days in a randomized order. Generally rats did not display any preference of arms in relation to their distance from the observer. The laboratory contained numerous visual cues; however, they were distributed unequally between the sides and in cases when the performance of a rat was impaired by the amnestic treatment, the arms extending in the direction of the side most rich in visual cues were clearly preferred (data not shown).

Experiment 1

Experiment 1 was undertaken after ten days of habituation time for the subjects with the animal house conditions and 20 h of fasting. Each animal was placed on the central platform of the radial arm maze and allowed to explore the maze until all the pellets at the ends of the arms were consumed or until 10 min had elapsed, whatever came first. Thereafter, the rat was weighed and given an injection of either saline, caerulein (100 ng/kg) or proglumide (1 mg/kg). Experiments were performed 5 days per week, from Monday to Friday. In addition to other measures, the number of pellets consumed and the latency until the animal picked up the first pellet were recorded in the first few experiments. Altogether 14 experiments were carried out in this series.

Experiment 2

In this experiment, the same animals were used after an additional training period of seven sessions, during which time no drugs were given. Rats were injected with different drugs on Tuesdays and Fridays before radial maze session. After injection, they remained in their home cages until the beginning of test. Treatments were randomized each time. The

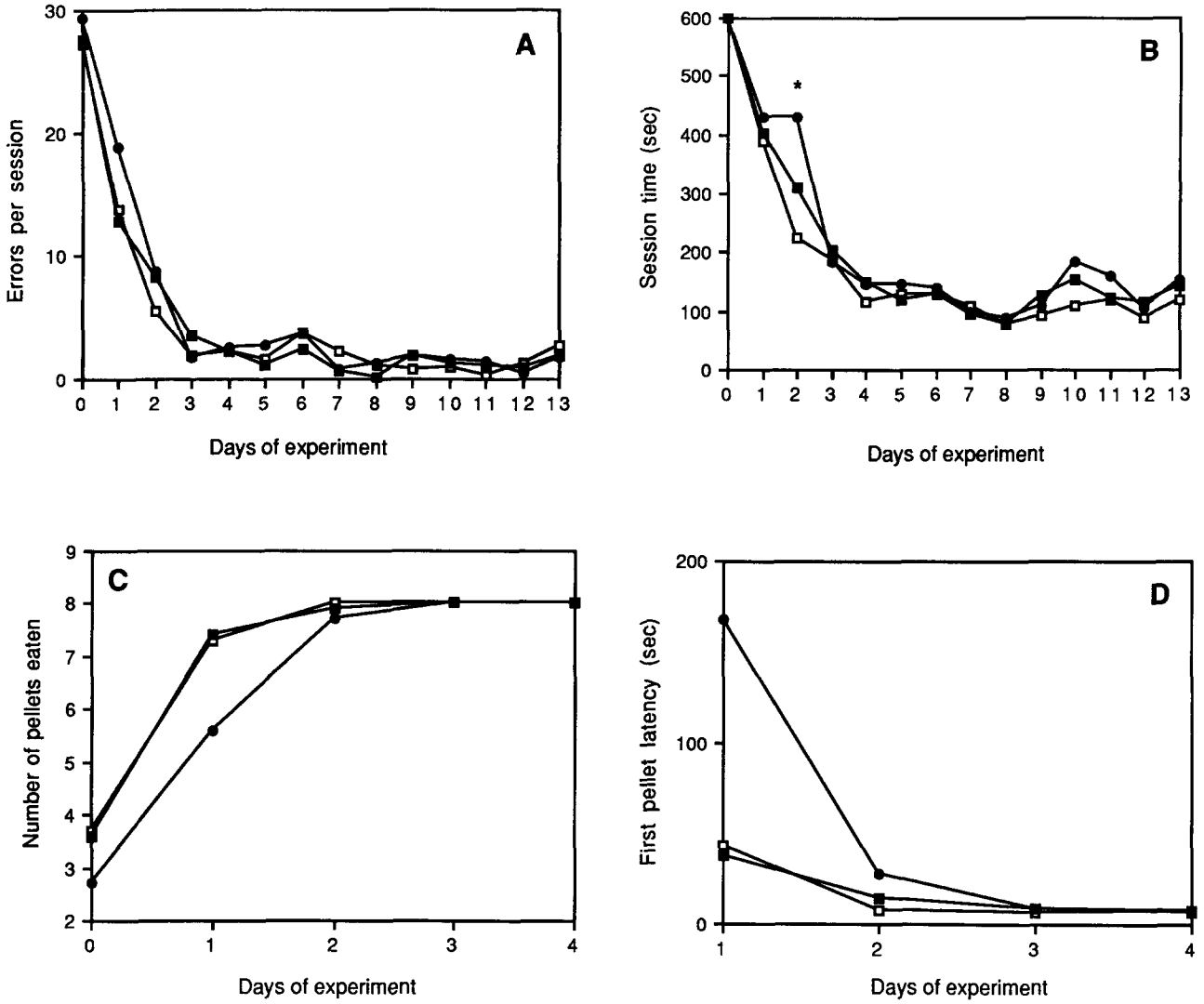

FIG. 1. The effects of 100 ng/kg caerulein (filled circles), 1 mg/kg proglumide (open squares) and saline (filled squares) on the number of errors made per session (A), on session time (B), on the number of pellets eaten during session (C) and on the eating latency (D) in the radial maze on different days during the training cycle. Day 0 corresponds to the first session after which the first drug treatment was carried out. Rats were tested undrugged each day and drugs were given after each session. Each data point represents the mean ± SEM of eight animals.
*$p < 0.05$ (significally different from both saline- and proglumide-treated rats).

number of injections was equal (i.e., 1 or 2) within each experiment for all the animals. Scopolamine is known to produce difficulties in eating dry food and, therefore, several investigators have substituted chow pellets with some other food for scopolamine experiments. However, as CCK has been shown to affect food-seeking behaviour depending on nutritive expectancies (16), we preferred to avoid changes in the physical features of food reward and, instead, baited the arms with small pieces of rat chow. At the dose 0.15 mg/kg used throughout this study, scopolamine did not produce obvious difficulties in eating. Neither had the small amount of food reward any diminishing effect on motivation: rats displayed similar behavioural pattern while the arms had been baited with bigger pellets; the performance was possibly additionally motivated by the eating session that always followed the test. On Mondays, Wednesdays and Thursdays, radial maze session was carried out without drug treatment. Recovery from the amnestic action of scopolamine was always complete on the session subsequent to drug experiment. Neither had any other drug any significant effect on memory functions on the following days.

Statistical Analysis

Results are expressed as means ± SEM. In Experiment 1, two-way analysis of variance (ANOVA) for repeated design was used, with post-hoc comparisons by Newman-Keuls test. In Experiment 2, one-way ANOVA and post-hoc Newman-Keuls tests were used with the exception that the data on the number of successive right choices were treated with Kruskal-

Wallis nonparametric analysis of variance together with post-hoc Mann-Whitney *U*-tests.

RESULTS

Experiment 1

During the first day of training as well as during the subsequent days, the behaviour of the rats in the radial arm maze closely resembled the original description of Olton and Samuelson (34). First, while exploring the arms, the rats frequently left the food pellets untouched and thereafter, they brought the pellets for eating to the central platform. Within a few days, rats began to eat at the place where the food was found. As shown in Fig. 1C, almost all pellets were consumed during the third session (Day 2), and subsequently the rats of all the three treatment groups (saline, caerulein, and proglumide) never failed to eat the pellets they had found. Two-way ANOVA did not reveal any significant Drug × Days interaction, and neither was there any significant drug effect. The latency time to pick up the first pellet varied a great deal during the initial experiments, especially in caerulein group (Fig. 1D). However, ANOVA did not reveal any significant difference between groups. On Day 3, all animals had a latency time less than 10 sec. The time needed to consume all 8 pellets decreased continuously, $F(2, 41) = 73.03$, $p < 0.0001$; and there was no significant Drug × Days interaction. However, there was a difference between drug treatments, $F(2, 41) = 4.89$, $p < 0.01$. Post-hoc comparisons demonstrated that on Day 2, the caerulein group spent significantly more time to reach all pellets than the control or proglumide group (Fig. 1B). At the same time, the number of errors made by the rats from all groups decreased continuously and was not significantly affected by drug treatment (Fig. 1A). Thus, on Days 1 and 2, the caerulein group had a tendency to differ from the control and proglumide groups, but in all but one case (see above) this difference missed the conventional level of significance ($p < 0.05$).

Experiment 2

As shown in Fig. 2, scopolamine produced a dose-dependent impairment of the performance in the radial maze, increasing the number of errors and the time per entry and decreasing the number of correct successive choices. All the effects were evident already at a rather low dose of scopolamine (0.15 mg/kg). In contrast, the CCK receptor antagonists proglumide (1 and 10 mg/kg) and devazepide (10 μg/kg and 1 mg/kg) were devoid of any influence on spatial memory (Table 1). Caerulein 10 and 100 ng/kg) and CCK-4 (25 and 50 μg/kg), the CCK receptor agonists, were also without effect (Table 1). An additional dose of caerulein, 1 μg/kg, was tested in a separate experiment, but the values obtained did not differ from controls (data not shown). The effect of scopolamine (0.15 mg/kg) was rather stable over all experiments conducted (Figs. 2–6). At the dose of 100 ng/kg, caerulein did not affect the action of scopolamine on the radial maze behaviour (Fig. 3). At the dose of 2 μg/kg, caerulein further increased the time per entry value (Fig. 4C). If the dose of caerulein was raised to 10 μg/kg, the amount of time per entry increased remarkably, and the number of successive right choices was lower if compared to the scopolamine group (Fig. 5). However, the number of wrong choices made was not different from the scopolamine group (Fig. 5A), and the potentiation of decrease in another measure of spatial memory, the number of successive right choices until the first error, was probably due to the sedative action of the high dose of caerulein. Indeed, some of the rats simply failed to produce more than 3–5 right choices, whereas they did not make any errors. CCK-4, at the dose of 50 μg/kg which did not affect spatial maze performance, significantly potentiated the increase in erroneous choices after scopolamine treatment (Fig. 6A). At the same time, the time per entry value did not change (Fig. 6C). In addition to the increased working memory impairment, some of the rats treated with scopolamine and CCK-4 (4 out of 8) had a peculiar pattern of maze exploration: after a right choice they oriented successively towards all other seven arms and finally re-entered the arm last chosen (1.3 ± 0.5 re-

TABLE 1

THE EFFECT OF PROGLUMIDE, DEVAZEPIDE, CAERULEIN, AND CCK-4 ON RADIAL MAZE PERFORMANCE IN TRAINED RATS

Drug/dose		Errors	Successive right choices	Time per entry
Vehicle		0.9 ± 0.4	7.0 ± 0.4	8.7 ± 0.4
Proglumide	1 mg/kg	0.6 ± 0.4	7.4 ± 0.5	8.7 ± 0.4
	10 mg/kg	0.4 ± 0.2	7.8 ± 0.2	9.3 ± 0.5
Vehicle		1.0 ± 0.3	6.6 ± 0.7	15.5 ± 2.4
Devazepide	10 μg/kg	1.0 ± 0.3	6.5 ± 0.4	12.5 ± 1.0
	1 μg/kg	0.9 ± 0.4	7.4 ± 0.2	13.2 ± 1.2
Vehicle		0.4 ± 0.2	7.1 ± 0.4	7.7 ± 0.6
caerulein	10 ng/kg	1.4 ± 0.2	6.4 ± 0.4	7.4 ± 0.4
	100 ng/kg	1.5 ± 0.4	7.1 ± 0.2	7.2 ± 0.6
Vehicle		0.8 ± 0.5	6.9 ± 0.6	12.1 ± 1.8
CCK-4	25 μg/kg	1.4 ± 0.7	6.2 ± 0.3	11.7 ± 1.1
	50 μg/kg	1.3 ± 0.4	6.4 ± 0.6	11.9 ± 0.9

Devazepide was administered 25–30 min and all other drugs 10–15 min before the experiment. ANOVA did not reveal any significant differences between groups in these experiments.

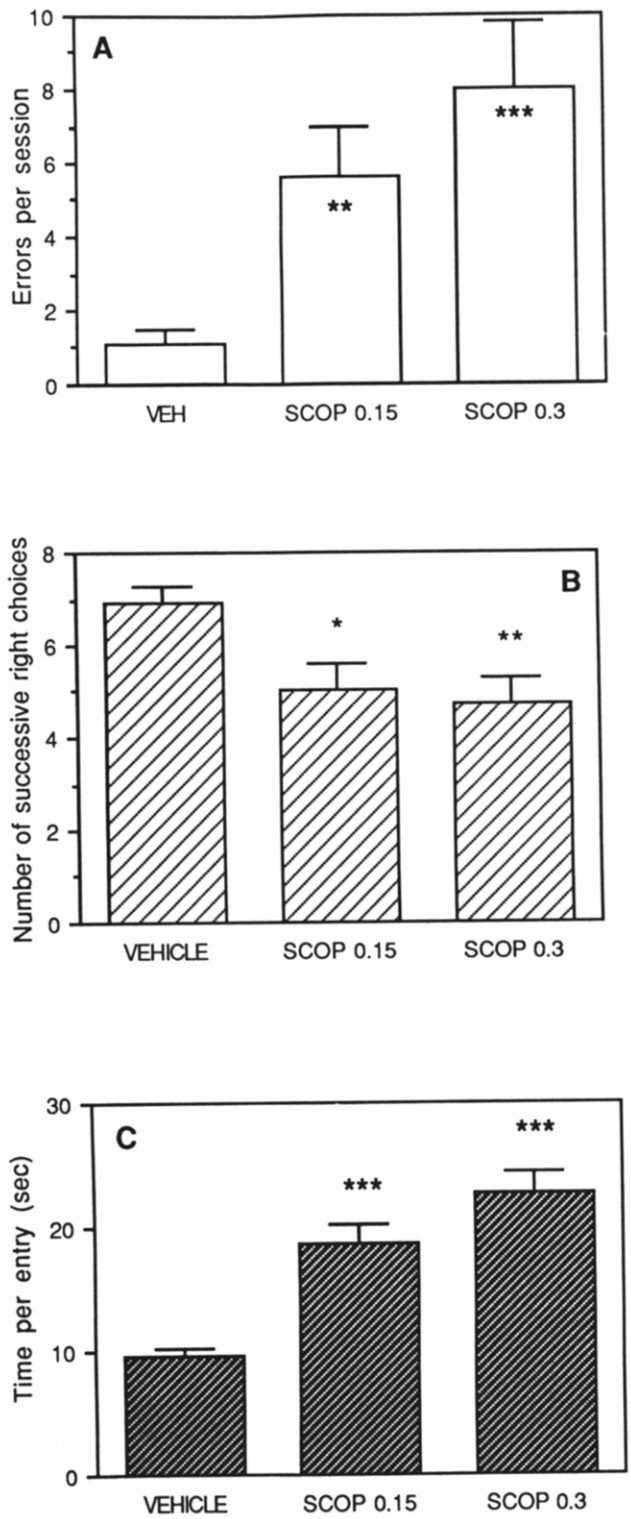

FIG. 2. The effects of 0.15 and 0.3 mg/kg scopolamine (SCOP) on the number of errors made per session (A), on the number of successive right choices until the first error (B) and on the time spent in maze per entry in seconds (C) in the radial maze test. Injections were given 20–40 min before the testing. Columns represent mean ± SEM for eight rats.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ (significantly different from Vehicle group).

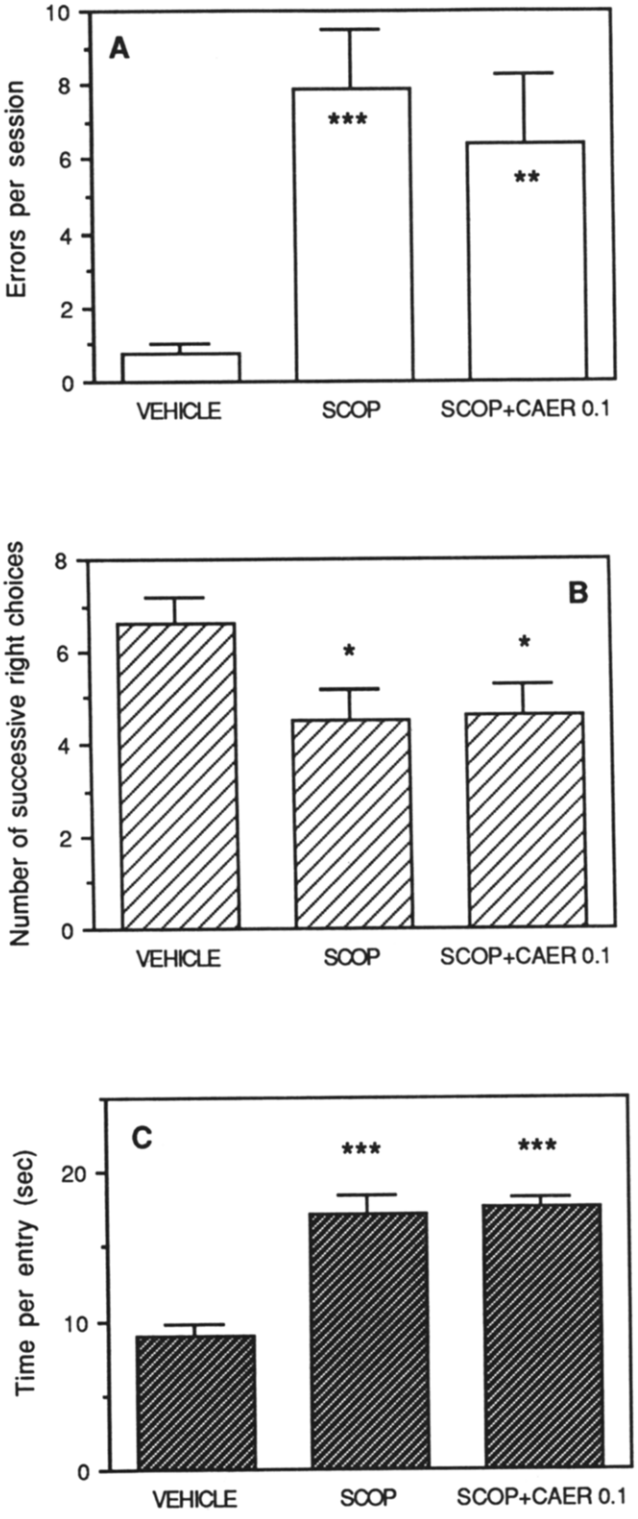

FIG. 3. The effects of 0.15 mg/kg scopolamine (SCOP) alone and together with 100 ng/kg caerulein (CAER) on the radial maze performance. (A) The number of errors made during the session; (B) the number of successive right choices until the first error; (C) the time spent in maze per entry in seconds. Scopolamine was injected 20–40 min and caerulein 10–20 min before the testing. Columns represent mean ± SEM for eight rats.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ (significantly different from vehicle group).

entries, mean ± SEM; Mann-Whitney U-test $p = 0.052$ as compared to controls or the scopolamine group after significant differences revealed in Kruskal-Wallis test with correction for ties). This was never observed in any of our experiments after scopolamine (or any other drug) as a single treatment.

DISCUSSION

In previous studies, CCK agonists have been found to improve memory functions and/or to prevent the action of various amnestic treatments. Furthermore, CCK receptor antagonists display an amnestic profile of their own. In this study, three issues were raised: are the memory consolidation effects of CCK receptor ligands necessarily linked to avoidance behaviour or can they be demonstrated in an appetitively motivated task (Experiment 1); do CCK agonists and antagonists influence spatial working memory; and finally, can the impact of CCK receptor subtypes be evaluated in such a paradigm (both Experiment 2). To answer these questions, several methodological points also will be discussed.

Exploitation of food-motivated tasks in studies on CCK receptors may seem complicated due to the satiety-related effects of CCK receptor agonists and antagonists (45), even if the doses of caerulein that improve memory (24) seem to be lower than those necessary for causing reduction in food intake. However, post-training administration of caerulein (a CCK receptor agonist) and proglumide (a CCK receptor antagonist) may, respectively, prolong or reduce the step-through latencies in passive avoidance tests on the following day(s) (14,26,39). Therefore, in our Experiment 1, the drugs were injected after the session and behaviour was observed on the following day. Eating per se seemed not to be influenced by the drugs, however, because even if food was accessible only in drugged state, rats treated with caerulein or proglumide did not develop any difference in weight as compared to controls (data not shown). This can be explained by the low doses of both compounds used and/or by the strong motivation caused by the restriction schedule. In any case, food motivation was probably not substantially affected by stimulation or blockade of CCK receptors under the present test conditions.

Uninterrupted radial maze task has been described to be rather resistant to pharmacological disruption, if "overtrained" animals have been used (8). However, scopolamine has been shown not only to disrupt working memory in well-trained animals, but also to prevent acquisition of the radial maze task if given daily during the training period (43). Proglumide, at a dose that reduces memory consolidation in passive avoidance tests, had no effect on learning of the radial maze task. On the other hand, treatment with caerulein caused some modest changes in behaviour. Although the number of errors made was similar every day in the caerulein and control groups, the caerulein-treated rats tended to be less successful in obtaining food pellets on Day 1, consuming less pellets and taking more time to pick up the first pellet; however, these differences just missed statistical significance. Caerulein increased significantly the time spent in solving the radial maze task on Day 2. The significance of these rather subtle behavioural changes induced by caerulein treatment at the beginning of the radial maze training may be small, but in any case they were not in direction one might expect from a memory-enhancing drug. Rather, the increased aversiveness of a novel environment after caerulein treatment (20) could be of importance. If this was the case, the observed changes would more

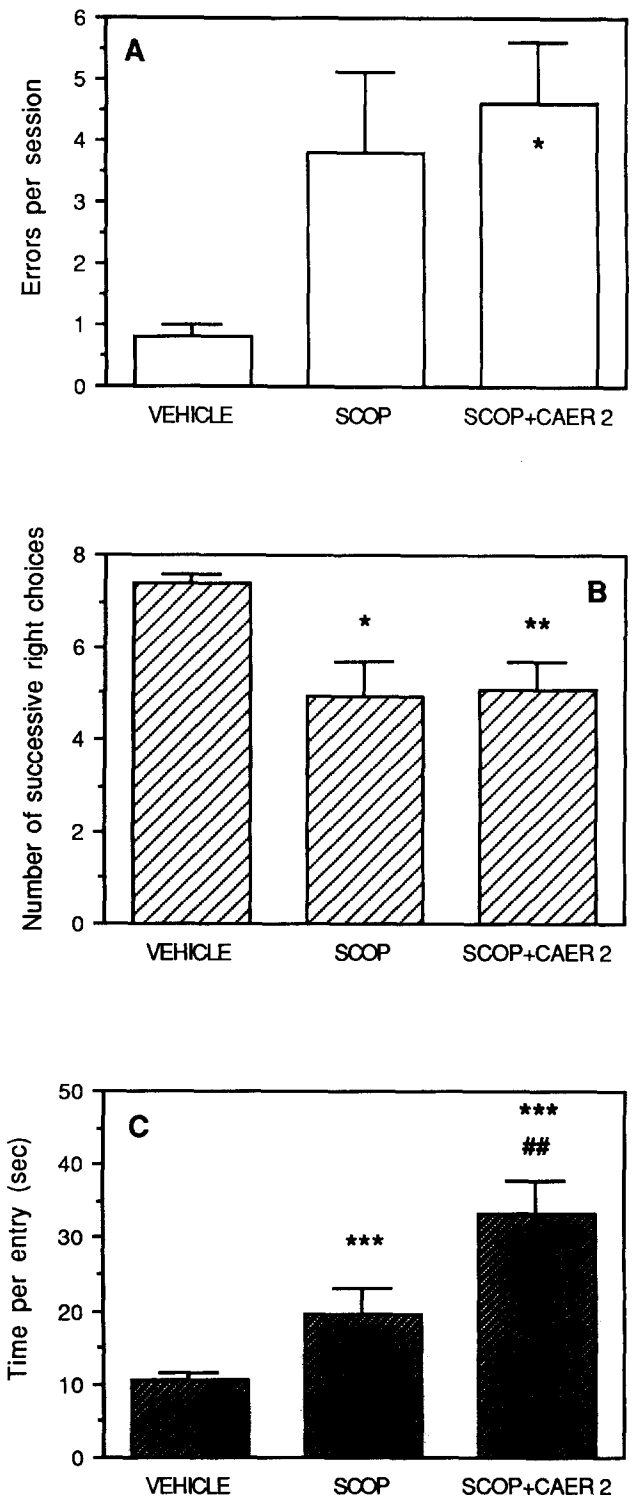

FIG. 4. The effects of 0.15 mg/kg scopolamine (SCOP) alone and together with 2 μg/kg caerulein (CAER) on the radial maze performance.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ (significantly different from vehicle group).
##$p < 0.01$ (significantly different from scopolamine group).

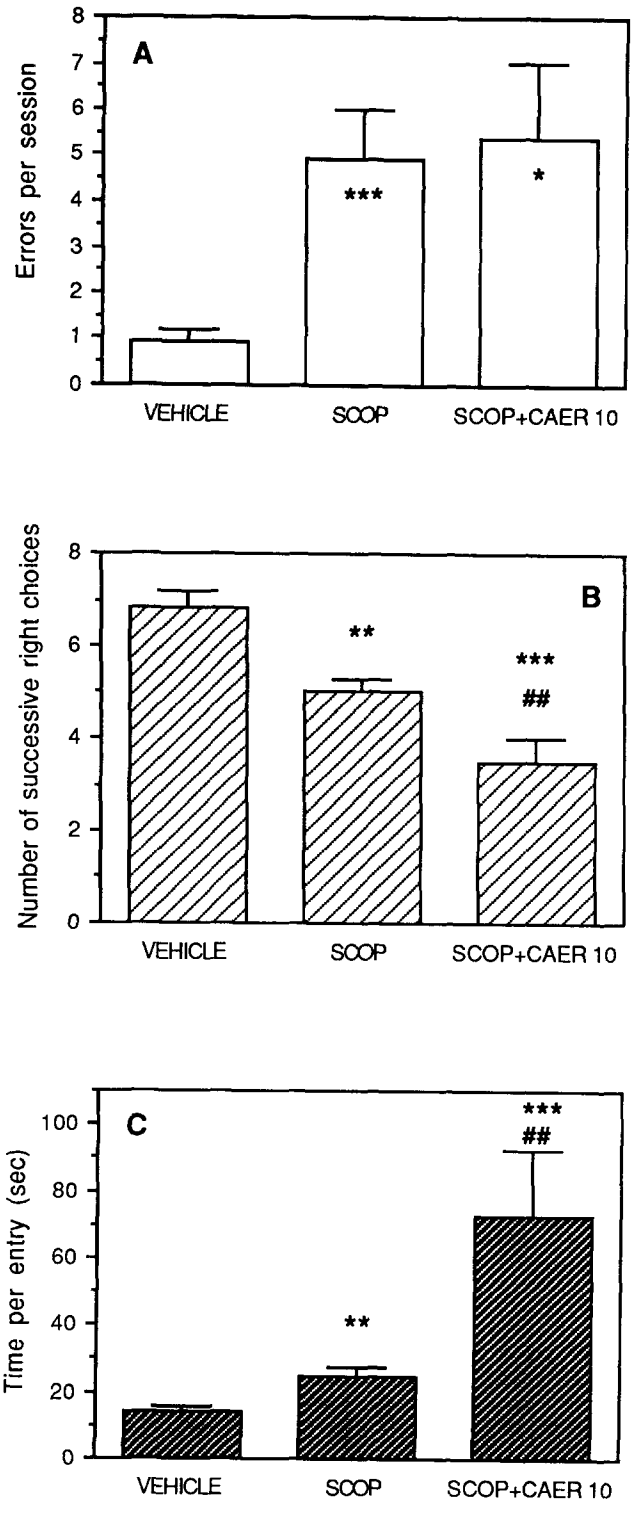

FIG. 5. The effects of 0.15 mg/kg scopolamine (SCOP) alone and together with 10 μg/kg caerulein (CAER) on the radial maze performance.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ (significantly different from vehicle group).
#$p < 0.01$ (significantly different from scopolamine group).

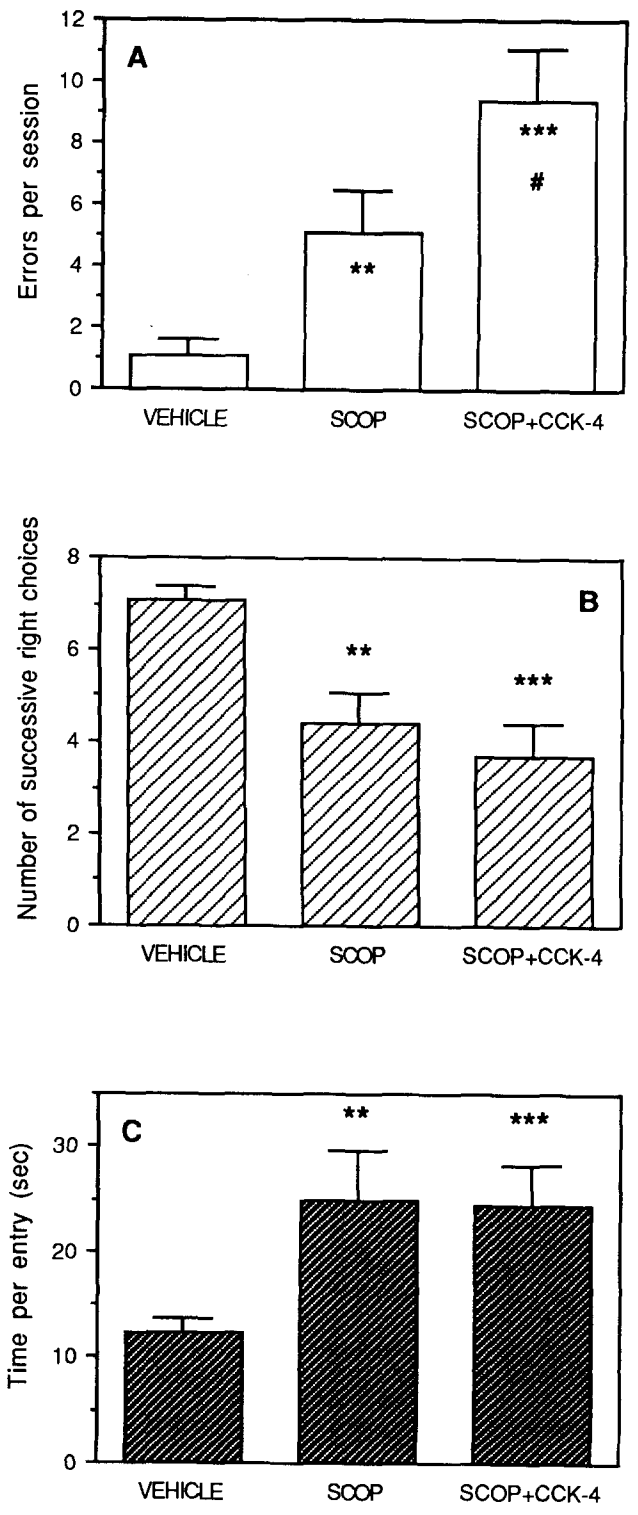

FIG. 6. The effects of 0.15 mg/kg scopolamine (SCOP) alone and together with 50 μg/kg CCK-4 on the radial maze performance. CCK-4 was given 10–20 min before the session.
**$p < 0.01$; ***$p < 0.001$ (significantly different from vehicle group).
#$p < 0.05$ (significantly different from scopolamine group).

likely refer to anxiogenic-induced hyponeophagia (18,38) than to a more general decrease in exploratory activity, since the number of arm entries was not changed. In summary, the results from the Experiment 1 suggest that CCK-receptor stimulation or blockade have no robust effect on memory consolidation in an appetitively motivated learning task.

Scopolamine is known to impair working memory in a radial maze task (31) as well as to inhibit memory consolidation in step-through avoidance paradigms (27). The latter effect can be blocked by peripheral injection of CCK-8 or caerulein (27). The CCK receptor antagonists proglumide and devazepide have also been reported to produce a pronounced memory deficit in passive and active avoidance tasks (25,39). In the present study, however, neither proglumide nor devazepide could impair the performance of rats in the radial maze task. It thus seems, that in avoidance training, endogenous CCK is released and the activation of CCK-A receptors facilitates memory consolidation, whereas spatial working memory as well as memory consolidation in the radial maze task are not dependent on CCK-ergic neurotransmission. In line with this, caerulein did not attenuate the amnestic action of scopolamine in the radial maze, even though it has been shown that scopolamine-induced deficits in passive avoidance can be reversed by caerulein treatment at a dose of 2 μg/kg (26). On the contrary, in the present study caerulein at higher doses increased the time used per arm entry. Moderate increases in this measure can also be observed after scopolamine treatment in parallel to an increase in errors made and should not be taken as a pure sedative effect (23); indeed, after treatment with amnestic drugs, the animals spend a considerable amount of time in orienting on the central platform. However, caerulein further increased the time per entry measure without producing potentiation of the effect of scopolamine on the number of errors. This finding appears to be in line with the well-established sedative action of caerulein and CCK-8 in the μg/kg dose range (11,45). After the dose of 10 μg/kg of caerulein, some of the animals were able to produce only 3–5 entries, whereas they did not make any errors. The sedative action of CCK-peptides is believed to be mediated through CCK-A receptors (11,30) and not to be related to CCK-B receptors (35). Consistently with this, CCK-4 (a CCK-B receptor agonist) treatment did not cause any increase in time used per entry, whereas the amnestic action of scopolamine was significantly potentiated. Along with this, the behaviour of the rats changed dramatically, if compared to single CCK-4 or even scopolamine treatment. After making one or two entries, some of the rats actively oriented towards different arms without entering them and then choosing the same arm they had entered last. This type of behaviour was unique to the scopolamine + CCK-4 group. In their home cages, as a rule, the well-trained rats approached the experimentator before the radial maze session (and subsequent feeding session), with an exception of the animals that had received scopolamine together with high doses of caerulein (and looked like sedated) or together with CCK-4. We would like to attribute these changes in rat behaviour to increased arousal and/or anxiety. CCK-4 has been demonstrated to induce panic attacks and severe anxiety in humans (5,6,12) and also to be anxiogenic in rats (22). Izquierdo and Medina (28) have recently theorized on GABAergic modulation of memory and have suggested that it is linked to the influence of anxiety level on memory functions. While moderate arousal may be beneficial, excessive arousal/anxiety has a negative influence on memory. There is reason to believe that this modulation is dependent upon the interference of the GABAergic and the CCKergic neurotransmission, since anatomical, physiological, and behavioural studies have suggested a GABA-CCK interaction, which functionally appears to be mutually antagonistic (see ref. 21 and references therein). The CCK receptors, which mediate modulation of GABA mechanisms related to anxiety, are probably of the CCK-B subtype. In support of this assumption, chlordiazepoxide, an anxiolytic benzodiazepine, attenuates the CCK-B receptor mediated promnestic effects (17). The importance of the degree of arousal for memory functions may explain the conflicting data (17,29) obtained with CCK-B agonists.

Repeated handling downregulates the sensitivity of animals towards anxiogenic drugs, including CCK-peptides (3,20); therefore, more puzzling than the lack of effect of CCK-4 alone in the radial maze test is the appearance of a distinct behavioural pattern after coadministration with scopolamine. This finding is not simple to interpret, but a hint can be found from a study on squirrel monkeys (19), in which benactyzine, another centrally active blocker of *m*-type acetylcholine receptors, dramatically potentiated alarm call rates induced by a presentation of a stressful stimulus. Thus, it seems reasonable to speculate that the scopolamine-caused inability to maintain a successful performance in the radial maze increases anxiety in a highly motivated food-seeking animal, making it more vulnerable to CCK-4 challenge. The failure of caerulein to induce an effect similar to CCK-4 is in line with several reports on a substantial difference in the effects of unselective CCK receptor agonists versus selective CCK-B receptor agonists (reviewed in ref. 24). The difference may be caused by distinct interactions with other neurotransmitter systems (1), ultimately leading to an antagonistic nature of CCK-A and CCK-B receptor-mediated actions (41).

In summary, our data show that the involvement of neuronal CCK in learning and memory functions depends upon the form of learning or memory under investigation. Furthermore, CCK-A and CCK-B receptors seem to play different roles. To reveal the physiological significance of CCK in memory, further studies should address these issues more explicitly.

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